Muscle Weakness in Persons with Multiple Sclerosis

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MUSCLE WEAKNESS IN PERSONS WITH MULTIPLE SCLEROSIS

A Dissertation Presented

by

LINDA H. CHUNG

Submitted to the Graduate School of the University of Massachusetts Amherst in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

September 2010

Kinesiology
MUSCLE WEAKNESS IN PERSONS WITH MULTIPLE SCLEROSIS

A Dissertation Presented

by

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DEDICATION

I dedicate this work to my family and Bernabé, who have always encouraged me to pursue great things. It is because of you guys that I have never stopped challenging myself and have reached this fantastic milestone in my academic career.
ACKNOWLEDGMENTS

For what seemed like an eternity to reach this major milestone, I have finally made it. The funny thing is it feels like it came too quickly. But I suppose that is what happens when you are surrounded by an amazing group of faculty and colleagues, all of whom have made me feel like a part of a family and whom I call my greatest friends. Thank you to my committee members for your unconditional support throughout this dissertation process. Thank you to the faculty and peers in the Department of Kinesiology for your support and unwavering enthusiasm. Special thank you to Stephen Foulis, Damien Callahan, Ryan Larsen, Ian Lanza, Danielle Wigmore, Mike Tevald and Anita Christie for your assistance in data collection, intellectual discussions, fond memories, and just good fun.

And last, but not least, a big THANK YOU to Jane Kent-Braun. Never have I ever had such an amazing advisor, who has guided me intellectually and supported me in my academic endeavors. You have provided me the confidence to take on anything that crosses my path. Thank you for being a great mentor and for showing me that one can have fun at work too. You are simply the best.
ABSTRACT

MUSCLE WEAKNESS IN PERSONS WITH MULTIPLE SCLEROSIS

SEPTEMBER 2010

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Skeletal muscle weakness is a problem for people living with Multiple Sclerosis (MS). Alterations in the central nervous system may be the primary source of muscle weakness because of the pathophysiology of MS. However, changes in peripheral mediators of force production may also contribute to muscle weakness in persons with MS. The main objective of the dissertation was to systematically identify key neural (motor unit discharge rates, spasticity) and muscular (muscle size, contractile function) mechanisms of force production that may explain lower isometric strength and dynamic power in persons with MS compared with age-matched controls. The knee extensor muscles of the weaker leg were studied, because this muscle group is commonly affected by MS.

We showed that persons with MS had lower peak isometric torque and dynamic power compared with controls. Persons with MS had lower motor unit discharge rates, smaller muscle size, and lower specific power compared with controls. There was no difference in passive torque (spasticity), specific strength, or maximal rate of force development between groups. Because differences in isometric strength between persons with MS and controls were abolished when torque was normalized to muscle
size, smaller muscle size may explain a large portion of lower isometric strength in persons with MS. Differences in dynamic power were reduced when peak power was normalized to muscle size, but remained lower in persons with MS compared with controls, suggesting that changes in neural factors (e.g., lower motor unit discharge rates) may explain lower dynamic power in persons with MS. These results suggest that different mechanisms may contribute to muscle weakness in MS, depending on the mode of contraction.

Lower motor unit discharge rates and smaller muscle size were identified as key mechanisms of muscle weakness in persons with MS. Each of these mechanisms has been shown to improve with resistance training in controls. Thus, this dissertation provides an evidence-based rationale for resistance training interventions in persons with MS, to improve isometric strength and power production by increasing motor unit discharge rates and muscle size.
PREFACE

Chapters 1 through 4 include the dissertation proposal, as submitted to the Graduate School in June 2009. In addition to the original proposal, the manuscript of Study 1 is included (Chapter 5). During a meeting with the dissertation committee in October 2009, it was decided that Study 2 would no longer be conducted as part of the dissertation. The reasons for this decision were first, Study 2 could not be undertaken until the completion of Study 1, which would provide the foundational evidence and rationale for Study 2; and second, an unreasonable amount of time would be needed to process and analyze the data from Study 1. Together, these factors rendered Study 2 impractical for inclusion in the dissertation. Rather, it was decided at this meeting to include a complementary study examining the energy cost of walking in persons with MS, which was not originally proposed in the dissertation. The manuscript for the energy cost of walking study is included as Appendix A.
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5.8 MS ($n=14$) had lower specific power across velocities compared with control ($n=11$; $p=0.05$). Data are mean ± S.D.
Multiple Sclerosis (MS) is an auto-immune disease affecting the central nervous system, which includes the brain and spinal cord. It has been estimated that 400,000 people in the United States and 2.5 million people worldwide are living with MS (National Multiple Sclerosis Society). Although the etiology of MS is unknown, environmental, infectious, and genetic factors are currently being investigated as possible causes of MS (54). Diagnosis of MS typically occurs in the second or third decade of life, and women are twice more likely to develop MS than men. The defining feature of MS is demyelination of nerves by T-cells, which disrupts the neural conduction of signals from the central nervous system to effector organs. As a result, inappropriate neural activity may lead to the onset of symptoms, such as muscle weakness and loss of postural control.

There are different forms of MS: primary progressive, relapsing-remitting, secondary progressive, and progressive relapsing. About 20% of initial diagnoses are primary progressive, which is characterized by a slow, continual worsening of symptoms. The most common form of initial diagnosis (~80%) is relapsing-remitting; people with this type of MS experience acute exacerbations of symptoms with periods of recovery. Within 10 years of diagnosis, about 50% of those who were initially diagnosed as relapsing-remitting will become secondary progressive, thus, transitioning to the characteristics of the primary progressive form. A rare form of MS is progressive
relapsing, which is a combination of the primary progressive and relapsing-remitting forms.

The diagnosis of MS follows stringent criteria (89), as symptoms may overlap with other pathologies. Therefore, confirmation of MS may take up to several weeks from the onset of symptoms. Recent technological advances (i.e., magnetic resonance imaging with gadolinium enhancement) have allowed for earlier diagnosis of MS (89). Clinical assessments include spinal taps and evoked potential tests. Spinal taps are collected samples of cerebrospinal fluid, which is used to determine the number or pattern of immunoglobulins that indicate the level of the immune response. Evoked potential tests of the visual, auditory, or somatosensory systems are performed to measure the magnitude and detection time of an electrical response to a given stimulus, which provides some insight to the quality of the nervous system.

The demyelination and sclera\(^1\) that define MS can develop anywhere in the white matter of the central nervous system. For that reason, MS is not limited to a particular region of the central nervous system. Common symptoms in MS include: changes in cognitive function, depression, symptomatic fatigue, muscle weakness, spasticity, dizziness, vertigo, vision problems, bladder and bowel dysfunction, difficulty in walking, balance problems, abnormal sensations, and pain (National Multiple Sclerosis Society). These detrimental symptoms may have a major impact on activities of daily living and overall quality of life in persons with MS.

\(^1\) sclera - scarring
Factors That Influence Muscle Strength and Power

Force generation is the product of a series of events that begins at the motor cortex of the brain and ends with the cycling of cross-bridges between myofilaments within the muscle. Impairments at any point along this pathway of force production may result in a decline in muscle strength\(^2\) and power\(^3\). Central factors of force production include the recruitment of motor units\(^4\), rate coding\(^5\), and adequate transmission of action potentials\(^6\) to the muscle.

There are a number of peripheral factors that may influence force production. Processes at the neuromuscular junction, such as the conversion of an electrical signal (action potential) to a chemical signal (acetylcholine), must be functioning. Excitability of the muscle membrane and propagation of the action potential along the muscle membrane and into the transverse-tubules are important in activating the muscle. Within the muscle, the rate of calcium release from the sarcoplasmic reticulum modulates the development of force production. Myosin ATPase activity, which is important in cross-bridge cycling, can affect the shortening velocity of contracting muscle fibers.

In addition to the aforementioned pathway, strength and power are also influenced by muscle size. Strength is partially affected by the number of muscle fibers in parallel, which is represented by muscle cross-sectional area (128). Power is

\(^2\) strength – isometric torque
\(^3\) power – product of torque and velocity
\(^4\) motor unit – a motor neuron and all of the muscle fibers it innervates
\(^5\) rate coding – modulation of motor unit firing rates
\(^6\) action potentials – nerve impulses
partially determined by the number of sarcomeres\(^7\) in series, which affects the maximal shortening velocity of a muscle fiber (128). Since fiber types differ in contractile velocity, fiber type distribution within a muscle may also influence power. The order of fiber types from slowest to fastest is: type I < type IIa < type IIx.

**Skeletal Muscle Weakness in Persons with MS**

One of the major problems for people with MS is muscle weakness. Lower extremity muscles are more affected by muscle weakness than upper extremity muscles in persons with MS (111). The decrease in torque in persons with MS ranges from 16 to 57% during both isometric (18; 80; 82; 83; 111; 113) and dynamic (3; 16; 21; 63; 99; 121) contractions. Reduced torque in persons with MS is often observed during dynamic contractions at high velocities (3; 45; 63; 99), suggesting the potential for power loss during high velocity contractions. Power asymmetry\(^8\) in the knee extensors is also observed in persons with MS (21).

The primary mechanism of muscle weakness may be central in nature and may be directly affected by the pathophysiology of MS. Demyelination of neuronal axons may prolong corticomotoneuron conduction time\(^9\), which is observed in persons with MS (50; 123). Central activation of the muscle (82; 106; 113) and specific strength\(^10\) (82) are lower in persons with MS (82; 106; 113) and may be a result of lower motor unit firing rates (33; 106) or poor motor unit recruitment.

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\(^7\) **sarcomeres** – the basic contractile units of the muscle fiber  
\(^8\) **Power asymmetry** – one leg being more powerful than the other leg  
\(^9\) **Corticomotoneuron conduction time** – the time it takes for the nerve impulse to travel from the brain to the muscle  
\(^10\) **specific strength** – the ratio of maximal voluntary force and the largest muscle cross-sectional area of the whole muscle
Over time, these central changes may affect peripheral mediators of force production, such as muscle size, fiber type distribution, contractile function, and processes at the neuromuscular junction\textsuperscript{11}. A decline in muscle cross-sectional area and altered processes at the neuromuscular junction would impact strength, while shifts in fiber type distribution and changes in contractile function may affect power.

Spasticity\textsuperscript{12} may also contribute to power declines in persons with MS.

There is some evidence that muscle atrophy occurs in persons with MS at both the whole muscle (57) and muscle fiber (44; 57) levels. However, the decrease in muscle size is not always observed in persons with MS (16; 82). There are discrepant findings with regard to fiber type distribution shifts in persons with MS, which may affect the velocity component of power. Persons with MS show either a higher percentage of type II fibers and lower percentage of type I fibers (57) or a lower percentage of type IIa fibers (44) compared to non-MS controls. Studies using electrical stimulation show that the rate of force development is similar (28; 30) or lower (82; 113) in persons with MS compared to non-MS controls, suggesting possible alterations in contractile function that may impede power production. However, at the muscle fiber level, unloaded shortening velocity (44) and myosin ATPase activity\textsuperscript{13} (17) are similar between persons with MS and non-MS controls, indicating that contractile function is unaltered in persons with MS. Processes at the neuromuscular junction, such as those that are involved in muscle membrane excitability, may be

\begin{itemize}
\item \textbf{processes at the neuromuscular junction} - these include, but not limited to, neurotransmitter release from the axon terminal and muscle membrane excitability
\item \textbf{Spasticity} – characterized as “a velocity-dependent resistance to passive stretch by the antagonist muscle due to the hyperexcitability of the stretch reflex” (64)
\item \textbf{myosin ATPase activity} – enzyme that hydrolyzes ATP to promote the “power stroke” of the myosin head, which drives cross-bridge cycling
\end{itemize}
altered in persons with MS. Prolonged recovery of the compound muscle action potential magnitude, a measure of muscle membrane excitability, following local curare treatment is observed in persons with MS (34).

Power deficits in persons with MS may also be explained by spasticity, which is another major symptom in MS. Spasticity is characterized as “a velocity-dependent resistance to passive stretch by the antagonist muscle due to the hyperexcitability of the stretch reflex”\textsuperscript{14} (64). Thus, co-activation\textsuperscript{15} of the antagonist muscle due to spasticity may slow the contraction velocity and lower power production of the agonist muscle, especially during high contraction speeds. Although spasticity is commonly assessed using subjective tests\textsuperscript{16}, very few studies have used quantitative measures of spasticity in persons with MS (88). Further, the role of spasticity in power production in persons with MS is not known.

By and large, there are a number of potential mechanisms that contribute to muscle weakness in persons with MS. The extent to which each of these mechanisms contributes to overall strength and power declines in persons with MS is not clear. Certainly, changes in the central mediators of force production may be the primary mechanisms of muscle weakness in persons with MS. However, there may be additional contributions from peripheral mediators, such as muscle atrophy and slower contractile function, that may explain strength and power declines in persons with MS.

\textsuperscript{14} stretch reflex – muscles spindles that detect changes in muscle length and stretch velocity excite the $\alpha$-motor neuron of the agonist muscle from which the muscle spindles lie, while inhibiting the $\alpha$-motor neuron of the antagonist muscle, thus preventing any further stretching of the muscle (Figure 1.1 describes the circuitry of the stretch reflex)

\textsuperscript{15} co-activation – as the agonist muscle performs a dynamic contraction, the muscle spindles of the stretched antagonist muscle becomes activated, and through the stretch reflex, the antagonist muscle becomes excited while the agonist muscle becomes inhibited

\textsuperscript{16} subjective tests – Ashworth or Modified Ashworth Scale (11)
Although central changes may affect peripheral mediators of force production, peripheral changes may also be a result of lower physical activity levels, which are observed in persons with MS (57; 81). Further, spasticity of antagonist muscles may play a role in lower power production in persons with MS. No studies have systematically examined a variety of potential mechanisms of muscle weakness in the same group of people with MS.

**Postural Control in Persons with MS**

Adequate integration and coordination of sensory and motor processes is important in postural control. The central nervous system receives input from sensory receptors regarding the body’s position in space via visual, vestibular, proprioceptive, and tactile cues, and processes this information to appropriately send motor commands to skeletal muscles, so that balance is maintained. Impairments in sensory reception, delivery of sensory input to the central nervous system, perception of sensory input in the brain, appropriate decision-making with regard to motor commands, and delivery of motor output to skeletal muscle may disrupt postural control.

Balance problems are another major symptom in MS, and there is a high incidence of falls in ~52% of MS patients (36). About 45% of MS patients use assistive devices for mobility, particularly those with a progressive type of MS (35). Some of the postural imbalances in persons with MS may be due, in part, to muscle weakness. Poor postural control may also be due to lesions that interfere with central processes that mediate postural control.

Postural control is commonly assessed using subjective measures. Clinical balance tests challenge patients to maintain postural control for 30 s during semi-
tandem, tandem, and single-legged stances. These tests reveal that persons with MS have difficulty with tandem and single leg stances (42; 116). In addition, persons with MS have poorly controlled balance responses to external perturbations (42). Lower physical activity levels shown in persons with MS (44; 57) may, partially, be explained by impairments in postural control.

Ground reaction forces\textsuperscript{17} are used to calculate quantitative measures of postural control, such as the center of pressure variability (130) and time-to-contact (105), in the anterior-posterior (AP) and medio-lateral (ML) directions. During quiet stance, the net center of pressure includes the time series of both the active ground reaction forces and the body’s center of mass projected on the ground (124; 130). The center of pressure variability is the spatial\textsuperscript{18} representation of postural sway over time. The time-to-contact incorporates both spatial and temporal\textsuperscript{19} aspects of postural sway, either from the center of pressure or center of mass, with respect to the base of support\textsuperscript{20} over time.

The center of pressure displacement during maximal leaning in the AP direction is lower in persons with MS compared to non-MS controls (53), indicating smaller boundary limits of stability in persons with MS. The center of pressure variability in the AP direction during quiet stance is greater in women with MS compared to women without MS (21), suggesting poor postural control in women with MS. Conditions challenging the sensory system (visual, somatosensory, vestibular, proprioception) show greater postural sway angles (79) and velocities (47) in persons with MS, especially when relying on the vestibular system alone.

\textsuperscript{17} ground reaction forces – measured forces, using a force plate, that are equal and opposite of the forces that are exerted by the feet
\textsuperscript{18} spatial – displacement
\textsuperscript{19} temporal – velocity and acceleration
Although measuring the center of pressure provides some information with regard to postural control, it does not fully describe the dynamics of postural stability\textsuperscript{21} in relation to the base of support. Time-to-contact may be a better measure for studying postural control in persons with MS, as it provides both temporal and spatial components of center of mass with respect to the stability limits\textsuperscript{22} during a given task. Time-to-contact is the estimated time a person would take to reach one’s stability limit before falling. There is limited information about time-to-contact as a measure of postural sway in persons with MS. Postural studies in the elderly (39; 124) and Parkinson’s Disease patients (125) show reduced time-to-contact compared to healthy controls.

Muscle strength is important in postural control (77; 109), especially during conditions when sensory systems are altered (66). A correlation between muscle strength and postural sway is observed in Parkinson’s Disease patients (77) and in stroke patients (66). Power asymmetry in the knee extensors is correlated with center of pressure variability in persons with MS (21). Bilateral resistance training of the knee extensors has shown increases in the percentage limits of stability\textsuperscript{23} during leaning trials in multiple directions in middle-aged and elderly adults (109). However, few studies have looked at the potential improvements in postural stability due to resistance training in persons with MS. These studies convey the importance of muscle strength and power on postural control.

\textsuperscript{20} **base of support** – area around the feet  
\textsuperscript{21} **dynamics of postural stability** – displacement of center of mass, velocity and acceleration of displacement of the center of mass  
\textsuperscript{22} **stability limits** – base of support  
\textsuperscript{23} **percentage limits of stability** – the furthest distance in which the center of gravity traveled from the mid-point with respect to the theoretical limits of stability computed by the Balance Master System
Overall, postural control is impaired in persons with MS. The examination of time-to-contact may be useful in understanding the dynamics of postural instability in persons with MS. The association between postural control and muscle strength needs further investigation in persons with MS, as these two systems are tightly coupled via the descending pathway of force production. Because MS presents impairments in central activation of the muscle, this may also affect postural control.

**Strength Training in Persons with MS**

Aerobic training programs have resulted in improvements in motor (45; 46) and cardiorespiratory (97; 102; 108) performance in persons with MS. Interestingly, spasticity is also ameliorated by an acute bout of unloaded leg cycling in persons with MS on (73) and off (74) anti-spasticity medication. Although these studies showed cardiovascular benefits, strength and or power gains from aerobic training are not always examined.

Resistance training is traditionally used to improve muscle strength directly, as it targets specific muscle groups. Neural adaptation and muscle hypertrophy are the primary mechanisms of muscle strength gains during short- and long-term resistance training, respectively (69). Potential mechanisms of neural adaptation include increased motor unit recruitment and rate-coding, better activation of synergist muscles, and reduction in co-activation of antagonist muscles (110).

Few studies have used resistance training programs in persons with MS. Home-based (31) and supervised (127) resistance training programs have produced improvements in strength, power, and measures of functional mobility (i.e., up-and-go test, number of steps within 3 minutes, walking speed). However, these studies did not
include a non-MS control group, which would have provided information regarding the
degree of change in strength, power, and functional mobility in persons with MS
following resistance training. Thus, it is not clear whether the response to resistance
training (i.e., changes in strength, neural adaptation, muscle hypertrophy) may be
blunted by MS.

The underlying mechanisms of strength and power gains in persons with MS are
not known. Because of the pathophysiological nature of MS, it is not clear whether
neural adaptations from 2 weeks of resistance training can occur in people with MS, nor
is it clear how the magnitude of these adaptations in persons with MS may compare to
persons without MS. In persons with no neurological impairment, increased motor unit
firing rates (52) and reduction in co-activation of antagonist muscles (49) have been
observed following resistance training. It is not known if 2 weeks of resistance training
will have a beneficial effect on postural control in persons with MS. If beneficial
effects are observed, this would imply that neural adaptations are enough to improve
balance in persons with MS.

**Significance of Dissertation**

Inadequate motor performance is a problem in persons with MS. The primary
mechanism of muscle weakness may partially be a compromised central nervous
system, which may further affect secondary mechanisms (i.e., muscle size, contractile
function, etc.). Further, power loss in persons with MS may also be exacerbated by the
presence of spasticity within the muscle. The contribution of all of the potential
mechanisms of muscle weakness is not clear, and an understanding of these
mechanisms of weakness will be useful in designing appropriate therapeutic interventions to improve muscle strength and power in persons with MS.

Muscle weakness may partially explain the limitations in performing functional tasks and maintaining postural control. Indeed, strength and power gains may place persons with MS further away from disability, so that normal daily activities can be performed and overall quality of life improved. However, it is not known if the resistance training response in persons with MS is blunted compared to persons without MS. This dissertation would provide some evidence with regard to the reversibility of the detrimental effects of MS using short-term resistance training. Further, benefits of resistance training may translate to greater postural control in persons with MS, indicating the importance of neural adaptations on balance.

**Study 1: Mechanisms of Muscle Weakness in Persons with MS**

The primary aim of this study is to determine the mechanisms of diminished strength and power in persons with MS. Lower strength in persons with MS may be attributed to muscle atrophy and lower motor unit firing rates. Spasticity and slow contractile function may also be important in lower power in persons with MS. An exploratory aim will examine the contribution of each of the mechanisms of force production in explaining muscle weakness. The knee extensors (KE) will be examined in this study, as these muscles are observed to be weak in persons with MS (3; 63; 99; 111; 121) and are important in activities of daily living24 (15; 21).

**Hypothesis 1.1** Maximal voluntary isometric contraction (MVIC) and peak power (highest power in the power-velocity relationship) of the KE will be lower in

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24 **activities of daily living** – such as stair climbing, rising from a chair, walking, etc.
persons with MS compared to non-MS controls, indicating muscle weakness in persons with MS.

Hypothesis 1.2 Motor unit firing rates (needle electromyography; pulses·s^{-1}) of the vastus lateralis muscle at 50% and 100% MVIC will be lower in persons with MS than non-MS individuals, suggesting that lower central drive to the muscle may contribute to strength and power loss.

Hypothesis 1.3 The ratio of voluntary-to-stimulated rate of force development (% peak torque·ms^{-1}) during an MVIC and specific strength (N·m per cm^{2}) will be lower in persons with MS compared to non-MS controls, indicating lower neuromuscular drive to the muscle in persons with MS.

Hypothesis 1.4 Muscle cross-sectional area (from magnetic resonance imaging; cm^{2}) of the KE will be smaller in persons with MS than non-MS controls, suggesting that a reduction in muscle size may contribute to strength and power loss.

Hypothesis 1.5 The rate of force development from a stimulated tetanus (% peak force·ms^{-1}) will be lower in persons with MS than non-MS individuals, suggesting that contractile function or excitation-contraction coupling may contribute to power loss.

Hypothesis 1.5 The ratio between passive torque from the hamstrings and voluntary torque from the KE at high velocities (>120°·s^{-1}) will be greater in persons with MS than non-MS individuals, suggesting that spasticity contributes to reduced power during high velocity contractions via co-activation of the antagonist muscle.
**Study 2: Resistance Training in Persons with MS**

**Aim #1**

The primary aim of this study is to determine the effects of 2 weeks of high-intensity resistance training (3 times per week) on muscle strength and power, motor unit discharge rates, and antagonist muscle co-activation in persons with and without MS. In persons without MS (C), strength gains during short-term training are primarily due to neural adaptations and not due to muscle hypertrophy (69). As MS is a central nervous system disease, it may be that neural adaptations (i.e., increased motor unit discharge rates and lower co-activation of antagonist muscles) are blunted during short-term resistance training compared to persons without MS. The KE will be examined in this study.

**Hypothesis 1:** Increases in KE strength (maximal voluntary isometric contraction, MVIC; % pre-training) and power (% pre-training) will be greater in C compared to MS following 2 weeks of resistance training, indicating a blunted response to resistance training in people with MS.

**Hypothesis 2:** Maximal motor unit firing rates (pulses·s^{-1}) of the vastus lateralis muscle during contractions at 100% MVIC will increase in both C and MS following 2 weeks of resistance training, indicating that neural adaptations occurred during resistance training.

**Hypothesis 3:** The change in maximal motor unit firing rates of the vastus lateralis muscle at 100% MVIC following 2 weeks of resistance training will be smaller in MS compared to C, suggesting blunted responses in motor unit behavior in persons with MS.
Hypothesis 4: Co-activation (%) will be lower in both MS and C following 2 weeks of resistance training compared to pre-training levels, suggesting more effective coordination of neural activation during contractions following training. Exploratory regression analyses will also be conducted to examine the extent to which neural adaptations explain changes in strength and power, as well as how strength and power improvements affect physical function. These results will provide evidence that short-term resistance training can increase muscle strength and power, as well as show that the nervous system of persons with MS has the capacity to improve with resistance training.

Aim #2

The secondary aim of this study is to investigate the effect of resistance training on postural control during 30 s of quiet and leaning (front, back, left, right) stances and physical function in persons with MS. Modest, non-significant decreases in postural sway were reported in persons with MS following a home-based resistance training program (31). During leaning stances in different directions, limits of stability increased in persons with no neurological impairment following resistance training (109). Better balance may translate to improve physical functioning. Since persons without MS have minimal balance problems and have adequate functional mobility, changes in postural control and physical function may be greater in MS compared to C.

Hypothesis 2.2.1 The net center of pressure variability (mm) and time-to-contact (s) during 30-second trials of quiet and maximal leaning (front, back, left, right) will decrease in both C and MS following 2 weeks of resistance training, suggesting improvements in postural control.
Hypothesis 2.2.2  The change in net center of pressure variability and time-to-contact during quiet and maximal leaning (front, back left, right) stances will be greater in MS compared to C, suggesting greater postural control improvements in persons with MS compared to non-MS controls following 2 weeks of resistance training.

Hypothesis 2.2.3  The change in 10s rapid foot-tap count, timed 10m walk, timed up-and-go test, and timed chair rises will be greater in MS compared to C, suggesting physical function improvements in persons with MS compared to non-MS controls following 2 weeks of resistance training.
Figure 1.1

Muscle spindles detect changes in muscle length and velocity. When activated, a muscle spindle (A) sends an impulse along the Ia afferent nerve (blue) and makes synaptic connections with the Ia efferent nerve of the agonist muscle (red) and the Ia inhibitory interneuron (green), which will make synaptic connections with the Ia efferent nerve of the antagonist muscle (purple). Simply, the stretch reflex excites the agonist muscle of which the muscle spindle resides and inhibits the antagonist muscle. Adapted from Human Anatomy and Physiology, Marieb 7th edition.
CHAPTER 2
LITERATURE REVIEW

Introduction

Muscle weakness is a common problem in MS (National Multiple Sclerosis Society), and alterations in the physiological processes that underlie voluntary force production may explain lower strength in persons with MS. Central processes\(^{25}\) that are directly affected by the pathophysiology of MS may be the predominating mechanisms of muscle weakness, which in turn may affect peripheral mediators of force production\(^ {26}\) and muscle size. Spasticity\(^ {27}\), another common problem in MS, may also decrease power through antagonist coactivation of spastic muscles (22). It is not clear what the major contributors of muscle weakness are in persons with MS.

Muscle weakness may play a role in reduced postural control and physical function in persons with MS. Short-term resistance training of lower extremity muscles may provide a means for improving postural control via neural adaptation in persons with MS. Neural adaptation is shown to contribute to early strength improvements (2 weeks) during a resistance-training program in young adults without MS (69). However, it is not clear whether neural adaptation is blunted in persons with MS because of the pathophysiology. In addition, it is unknown whether short-term resistance training can improve postural control in persons with MS. The aim of this

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\(^{25}\) **central processes** – such as motor unit firing rates, motor unit recruitment, conduction of neural impulse

\(^{26}\) **peripheral mediators of force production** – such as neurotransmitter release at the neuromuscular junction, muscle membrane excitability, propagation of neural impulse along the sarcolemma, calcium release from the sarcoplasmic reticulum, cross-bridge cycling

\(^{27}\) **spasticity** - characterized as a velocity-dependent resistance to passive stretch by the antagonist muscle due to the hyperexcitability of the stretch reflex (64)
chapter is to present existing literature on potential mechanisms of muscle weakness, functional mobility, postural control, and resistance training in persons with MS.

**Sources of muscle weakness in persons with MS**

**Central Nervous System**

The integrity of myelin sheaths, which insulate neurons of the central nervous system, is crucial in ensuring adequate delivery of central impulses to effector organs. Myelin sheaths are layers of phospholipid proteins that surround neuronal axons to promote quick transmission of action potentials along the nerve via saltatory conduction. Also, myelin sheaths are dielectric\(^{28}\), preventing the electrical current from leaving the axon – much like the rubber insulation surrounding a copper wire.

A hallmark of MS is the demyelination of neurons. Demyelination affects the central transmission of afferent (sensory) and efferent (motor) impulses. Conduction blocks may arise and signal transmission failure may occur due to a reduction in the safety factor\(^{29}\) for impulse transmission in demyelinated and lesioned neurons (62; 84). Clinically, a marked reduction in the amplitude or area of an evoked action potential may indicate the presence of a conduction block in patients with neuropathological diseases (23). Axonal damage in demyelinated areas of the neuron has been observed in persons with MS, using magnetic resonance imaging and magnetic resonance spectroscopic imaging (78). If severe axonal damage leads to Wallerian degeneration, a decrease in motor unit size and number may occur, which in turn may decrease force production. However, no studies have examined motor unit size and number in persons with MS.

\(^{28}\) dielectric – non-conducting
Central activation of the muscle plays a key role in voluntary force production. Voluntary movements are initiated at the motor cortex through the transmission of impulses along efferent pathways that recruit motor units. The central regulation of muscle force primarily involves the rate at which central impulses excite the muscle (i.e., motor unit firing rate, MUFR) and the recruitment of motor units. Intramuscular electromyography (EMG) is a technique used to record individual motor unit firings via a needle electrode within the muscle. Compared to non-MS controls, motor unit firing rates are lower (33; 106) and highly variable (33) in persons with MS. In contrast, the magnitude of surface EMG activity during force production from 10% to 70% of MVC is greater in persons with MS compared to non-MS controls (83). It has been suggested that the increased EMG activity may be due to greater motor unit recruitment as a compensatory mechanism to overcome lower motor unit discharge rates in persons with MS (83). Although indirect evidence suggests alterations in motor unit recruitment in persons with MS, no direct measures of recruitment thresholds have been conducted in this population.

Transcranial magnetic stimulation is used to examine the transmission of these impulses by recording the corticomotoneuron conduction time\textsuperscript{30}, as well as the amplitude and area of the impulse that reaches the muscle (motor evoked potential, MEP). Studies using transcranial magnetic stimulation of the brain show prolonged corticomotoneuron conduction time (43; 123) and lower MEP amplitude and area (43) in persons with MS compared to non-MS controls. Abnormalities in MEP amplitude and area are shown to be more frequent in MS patients with higher disability (Expanded

\textsuperscript{29} \textbf{safety factor} – the difference between the threshold and peak amplitude of an action potential
Bonfiglio et al. (12) demonstrated that the cortical relay of impulses within the cerebrum may be altered in persons with MS, in that the prolonged delay in conduction time is primarily due to alterations in transcortical transmission rather than either afferent and efferent nerve transmission. The cortical relay time was unrelated to the disease duration of MS (12). Prolonged absolute and relative refractory periods are also observed in MS patients (10). Together, these studies suggest that impaired central activation via prolonged delivery and reduced amplitude of impulses may affect excitation of motor units and may partially explain reduced force production in persons with MS.

The level of central activation to the muscle can also be examined non-invasively at the periphery by using the following methodologies: central activation ratio, specific strength, and rate of voluntary force production. Central activation ratio is the maximal voluntary force relative to the total force produced during the superimposition of an electrical stimulus or train of stimuli during a maximal voluntary contraction (MVC) (55). Central activation failure can be determined by observing an increment in force during the superimposed stimuli on the MVC. Specific strength is the force per muscle cross-sectional area and allows the determination of muscle quality, independent of muscle size. Rate of voluntary force development during a MVC is expressed as the percent change in peak force over time and provides some indication of neuromuscular drive and contractile properties.

Lower central activation ratio (28; 82; 113) and rate of force development (82) are observed in persons with MS compared to non-MS controls. There is a modest

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30 **corticomotoneuron conduction time** – the time it takes the impulse to travel from the motor cortex to the muscle
decrease in specific strength of the ankle dorsiflexors in persons with MS compared to non-MS controls (82), but this is not always observed (57). In rats infected with experimental allergic encephalomyelitis\textsuperscript{31}, specific strength of the medial gastrocnemius is lower compared to controls (29). Interestingly, lower specific tension\textsuperscript{32} in type I fibers is observed in persons with MS, suggesting that there may be alterations at the myofilament level (44). The inconsistent results of specific strength may be a result of greater variability of specific strength among persons with MS compared to non-MS controls. It may be that declines in specific strength are more evident in other muscle groups.

In summary, the pathophysiology of MS has an impact on central factors that influence the activation of skeletal muscle. Central regulation of force production, amplitude and area of action potentials, and corticomotoneuron conduction time appear to be altered in persons with MS compared to non-MS controls. Thus, these changes in the central nervous system may partially explain muscle weakness in persons with MS.

**Neuromuscular Transmission**

Neuromuscular transmission involves the translation of a neural signal to a neurotransmitter signal, which in turn translates into an electrical signal at the muscle. Specifically, an action potential at the axon terminal causes the release of acetylcholine that crosses the synaptic cleft and binds to receptors at the motor end plate. This causes depolarization of the muscle membrane, and if depolarization reaches a threshold, it will generate an action potential that will propagate along the sarcolemma and into the

\textsuperscript{31} experimental allergic encephalomyelitis – animal model for multiple sclerosis
\textsuperscript{32} specific tension – force produced by a single muscle fiber
transverse-tubules. Failure in any of the aforementioned events could inhibit force production.

Amplitude of evoked potentials at the ulnar nerve during a short train of stimuli is lower in MS patients compared to non-MS controls (94), indicating some alteration in neuromuscular transmission. Evoked potential amplitudes following administration of anticholinesterase therapy, which minimizes the breakdown of acetylcholine in the synaptic cleft, are improved in persons with MS (94), suggesting that neurotransmitter release or its effect on receptors is impaired. Following local treatment of curare, recovery of evoked potential amplitudes is slower in people with MS compared to controls (34), signifying that impairments in neuromuscular transmission may be due to alterations at the receptor level of the motor end plate. However, persons with MS with spasticity show minimal depression of the H-reflex response following a slow stretch of the soleus muscle, as well as greater facilitation of the soleus H-reflex response compared to controls, indicating decreased presynaptic inhibition (85). Collectively, these studies show that neuromuscular transmission is changed in persons with MS and could affect force production.

Muscle Size

Muscle size is important in strength and power production. Both number and area of muscle fibers contribute to overall force production. Declines in whole muscle (57) and single muscle fiber (44; 57) cross-sectional area (CSA) are observed in persons with MS. However, size differences at the whole muscle (82) and fiber level (16) are not always observed in persons with MS. These discrepancies may be explained by

33 curare - temporarily blocks nicotinic acetylcholine receptors on the motor end plate
increased data variability in persons with MS, which may be, in part, due to different degrees of disability and physical activity levels.

The distribution of slow- and fast-twitch fibers may play a role in the velocity component of power production, as fast-twitch fibers have greater shortening velocity than slow-twitch fibers. Using the myosin ATPase staining technique, a higher percentage of type IIa fibers and a lower percentage of type I fibers in the tibialis anterior muscles were observed in MS patients compared to controls (57). In contrast, when fiber type distribution is determined by gel electrophoresis and silver-staining techniques, MS patients had a lower distribution of type IIa myosin heavy chain (MHC) isoform (44) and greater distribution of type I/IIa/IIx MHC isoforms in MS (16) in the vastus lateralis muscle. These discrepant results may be due to the different muscles studied and the analytical approaches used in identifying fiber types. Nevertheless, there appears to be a shift towards slow-twitch fibers, as well as a greater percentage of hybrid fibers in persons with MS.

The unloaded shortening velocity of type I and type IIa fibers (44) and the myosin ATPase activity for each fiber type (17) were similar between persons with MS and non-MS controls. These data suggest that the rate of cross-bridge cycling is unaltered in persons with MS. Interestingly, Garner et al. (44) found that specific tension was lower in type I, but not type IIa, fibers in persons with MS, suggesting that there may be an alteration in the number of cross-bridges or force per cross-bridge in type I fibers.
**Contractile Function**

Contractile function during voluntary contractions is influenced by central\(^{34}\) and peripheral\(^{35}\) factors. As described earlier, changes in central activation occur in persons with MS, and these central changes may bring on a cascade of changes within the muscle. Some studies examining contractile function in the periphery indicate lower rates of force development (113) and slowed force relaxation (82; 113) during electrically stimulated contractions in persons with MS, while other studies do not (28; 30). There is a leftward shift in the torque-velocity relationship in lower extremity muscles (82) but not in upper extremity muscles (30) in persons with MS compared to non-MS controls, suggesting a slower muscle profile in muscles that work against gravity.

Contractile velocity, important in power\(^{36}\) production, may be altered in persons with MS. Spasticity, a common symptom in MS, may impede high contractile velocity due to the hyperexcitability of the stretch reflex (see Spasticity). At the muscle fiber level, spastic muscles have shorter fiber lengths compared to non-spastic muscles (41), signifying a lower number of sarcomeres in series, which would affect contractile velocity. Increased muscle stiffness\(^{37}\) is also observed at the whole muscle (114) and muscle fiber (41) levels. Thus, muscle stiffness may play a role in lower power production due to the increased difficulty to generate fast contractile velocities.

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\(^{34}\) central – i.e., motor unit discharge rates  
\(^{35}\) peripheral – i.e., fiber-type distribution, calcium kinetics, fiber length (number of sarcomeres in series)  
\(^{36}\) power – product of torque and velocity  
\(^{37}\) stiffness - resistance to passive movement that may be due to non-reflex mechanisms
Spasticity

Spasticity is defined as a “motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) due to the hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome” (64). The stretch reflex arc encompasses the muscle spindle, the afferent nerve to the spinal cord, and the disynaptic connections to the Ia efferent nerve of the agonist muscle and the Ia inhibitory interneuron (which will make a synaptic connection with the Ia efferent nerve of the antagonist muscle). Simply, the stretch reflex excites the agonist muscle (the muscle that is being stretched) while inhibiting the antagonist muscle. The mechanism of spasticity is still debated, but the hyperexcitability of the stretch reflex may be due to dis-inhibition at the presynapse (e.g., diminished neurotransmitter release to the Ia motor neuron) and or reduced disynaptic reciprocal Ia inhibition (e.g., lower inhibition of the antagonist muscle) (68; 86).

A common clinical assessment of spasticity is the Ashworth or modified Ashworth scale (11). In these techniques, clinicians manually move the limb segments and make judgments based on how resistant the joint movement is. The subjective nature of these tests relies heavily on clinical experience. And it is difficult to discern what is mediating increased passive resistance, structural (non-reflex) or neural (reflex) alterations.

Quantitative methods using biomechanical and or electrophysiological instruments have been developed to improve measures of spasticity in patients. Passive torque (dynamometer), oscillation decay (pendulum test), H-reflex, and stretch reflex are used as indices of muscle spasticity (9). Passive torque is the torque produced by a
muscle that is passively stretched by the dynamometer. The pendulum test uses a
goniometer to measure oscillation decay of the knee joint when the relaxed leg is
released from full extension and is allowed to swing freely. The H-reflex is a surrogate
measure of motor neuron excitability. By electrically-stimulating the nerve, the
maximal amplitude of the H-wave can be determined using surface electromyography
(EMG). The stretch reflex is the EMG signal obtained in response to the stretching of
the muscle. Although there are many ways to quantitatively measure spasticity, there is
no gold standard. The combination of biomechanical and electrophysiological
measurements may provide a more complete evaluation of spasticity by examining the
relationship between stretch velocity and passive torque, and the stretch reflex
threshold, respectively (9).

Numerous studies have used a quantitative approach to assess muscle spasticity
in stroke (4; 98) and spinal cord injury patients (37; 51; 76; 96; 100). Likewise, several
studies have measured spasticity quantitatively in persons with MS (8; 87; 88; 90).
Increased passive torque with increasing speed of passive movement (90) and
dampened oscillation decay (8) at the knee joint are observed in persons with MS.
Increased stretch reflex amplitude with increasing velocity and lower stretch reflex
threshold (i.e., the velocity at which passive torque is detected) of the soleus are
observed in MS patients (87; 88).

Coactivation of the antagonist muscle, as a result of spasticity, during a
voluntary dynamic contraction, may impede power production of the agonist muscle.
Corcos et al. (22) showed a stretch reflex-induced coactivation of the soleus during
dorsiflexion in spastic patients. Musampa et al. (75) also observed stretch reflex-
induced coactivation of the stretched muscle during elbow extension in stroke patients. It remains unclear if stretch reflex-induced coactivation plays a role in lower force production in persons with MS, particularly during high velocity contractions.

**Summary: Sources of muscle weakness in persons with MS**

Overall, there are many factors that may explain muscle weakness in persons with MS. These include neural alterations at the central and peripheral levels, changes in contractile function, muscle atrophy, changes in fiber-type distribution, spasticity, and coactivation. However, the contribution of each of these factors to muscle strength and power in persons with MS is not well understood.

**Physical Function and Postural Stability in MS**

**Postural control**

Studies have shown that postural control in MS is compromised. Persons with MS exhibit reduced anterior and posterior center of pressure displacements when leaning compared to non-MS controls (53). Women with MS have greater center of pressure variability in the AP direction and greater load asymmetry\(^{38}\) during quiet stance compared to non-MS women (21). When one or more sensory systems (visual, somatosensory, vestibular, proprioception) are perturbed, persons with MS demonstrate greater postural sway (79). Postural sway velocities in the AP and ML directions during quiet stance on stable and foam rubber support surfaces are greater in persons with MS compared to non-MS controls (47).

Postural control may be better measured by time-to-contact, which provides temporal and spatial information about center of mass relative to the stability boundary,

\(^{38}\) **load asymmetry** – differences in the ground reaction forces between feet
than spatial measurements, e.g., center of pressure variability. However, time-to-contact has not been measured in persons with MS. In studies of aging, older adults exhibit lower time-to-contact in the AP (39; 124) and ML (124) directions during leaning tasks compared to younger adults. In Parkinson’s Disease patients, time-to-contact in the ML direction is lower compared to healthy controls (125). Time-to-contact may be useful in achieving a comprehensive description of postural control in persons with MS.

Gait

Physical function and postural stability are important in maintaining activities of daily living. Persons with MS have slower gait speeds (16; 21; 67; 70; 91; 111; 121), consisting of shorter stride lengths, decreased cadence, and prolonged double-support phase during the gait cycle (7; 67). Further, joint angles during the gait cycle are also altered in minimally-impaired persons with MS (7; 67). Olgiati et al. (93) showed high energy costs of walking on a treadmill in persons with MS compared to non-MS controls, which was associated with knee flexion-extension time (their spasticity measure) in MS patients (91).

In addition to slow walking speeds, women with MS have greater difficulty initiating gait (104). Minimal displacement of the center of mass (due to a slow anterior velocity in the anticipatory postural adjustment) and smaller posterior shift in the center of pressure during gait initiation were observed in women with MS compared to non-MS controls. These data suggest that persons with MS may have a functional strategy to stay within their stability boundaries39 until necessary to make the first step (104).

39 stability boundaries – the perimeter of balance
**Effect of muscle strength on postural control and physical function**

Muscle strength is important in postural control, which in turn is necessary for the performance of activities of daily living. Muscle strength and postural control are linked in that they share the same descending pathway in the nervous system to activate skeletal muscle. There are very few studies directly examining the role of muscle weakness in postural control in persons with MS. Chung et al. (21) observed a correlation between power asymmetry in the knee extensors and center of pressure variability in persons with MS. In stroke patients, Marigold et al. (66) observed associations between strength and postural sway when patients had to rely only on their vestibular system. Correlations between muscle strength and postural sway velocity during quiet stance are observed in Parkinson’s Disease patients (77). When strength is improved by bilateral resistance training of the knee extensors, middle-aged and older adults increased their limits of stability during leaning trials in different directions (109).

Muscle strength also plays an important role in physical function. Leg power is predictive of functional mobility and performance in the elderly (5; 26). In MS patients, gait speed is associated with muscle strength (120), particularly in patients who have both pyramidal and sensory impairments (121). Recently, knee extensor power asymmetry was correlated with self-selected, normal and brisk walk times in persons with MS and non-MS controls, suggesting that asymmetrical weakness may play a role in physical dysfunction in persons with MS (21).
Summary: Physical function and postural stability in MS

Overall, physical function and postural control are compromised in persons with MS. Slow walk speeds, altered gait kinematics, and prolonged gait initiation in MS patients indicate a functional strategy to minimize the risk of falls. Greater postural sway in persons with MS suggests difficulties in maintaining balance control. The inclusion of time-to-contact may give a better description of postural control changes in persons with MS, as it includes both spatial and temporal components of postural control. The relationship between muscle strength and postural control needs further investigation in persons with MS. It is not clear whether strength gains from resistance training would improve postural control in persons with MS.

Effect of resistance training on motor performance in MS

Resistance training is an effective way of improving strength and power in targeted muscle groups. There are a number of systemic changes that contribute to strength gains during long-term resistance training. A classic paper by Moritani and DeVries (69) showed both training-induced neural and morphological contributions to strength gains in young, healthy adults, each contributing more to increased strength at different phases of the resistance training period (Figure 2.1). Neural adaptations contributed about ~80% during early strength gains at week 2. However, its relative contribution declined as muscle hypertrophy’s contribution to strength gains increased after 4 weeks of training. Potential mechanisms of neural adaptation to strength training are: 1) complete activation of the prime mover by increased motor unit recruitment and firing rates, and 2) appropriate activation of synergist and antagonist muscles (110). Motor unit firing rates are increased within the first 2 weeks of resistance training in the
elderly, who had lower motor unit firing rates compared to young adults at baseline (52).

There are limitations to Moritani and DeVries work. Neural adaptation was monitored using integrated, surface EMG signals. Muscle hypertrophy was measured by taking the largest leg circumference. A better approach would be to measure neural adaptation using intramuscular EMG for motor unit firing rates and magnetic resonance imaging (MRI) for muscle cross-sectional area. Nevertheless, Moritani and DeVries demonstrated that 2 separate mechanisms (neural and muscular components) contribute to strength gains during resistance training.

There are several studies that have used resistance training in persons with MS. DeBolt et al. (31) observed increased leg power (sum of both leg extensors) following an 8 week home-based resistance training (3x/wk for 30min) using weighted vests and ankle cuffs. White et al. (127) observed strength gains in the knee extensors and plantarflexors, but not in the knee flexor muscles, following an 8 week resistance training (2x/wk for 30min) using weight machines (ramp protocol; intensity ranging from 50% to ~70% MVC). Taylor et al. (118) showed increases in arm and leg press 1RM, following 10 weeks of progressive resistance training (2x/wk for 60min). In addition to strength or power gains, persons with MS had modest-to-moderate improvements in physical function, such as decreased time in the up-and-go test (31), increased number of steps over a 3 min period (127), muscular endurance (118), and improved gait kinematics (40) (48). It is not clear whether these gains in strength and power are comparable to non-MS controls, as no non-MS control groups were used in

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40 improved gait kinematics – decreased time in the double-support phase and stride length in the gait cycle
the above-mentioned studies. It is unknown whether greater gains in strength and power would have been observed if strength and power were measured using the same contraction mode as training. Also, potential mechanisms that may explain for increased strength and power were not examined in these studies.

The underlying mechanisms that contribute to improvements in muscle strength and power in persons with MS are not known. Neural adaptation may occur through short-term resistance training and may potentially reverse or slow the detrimental effects of MS. Häkkinen et al. (49) observed a reduction in coactivation of antagonist muscles in the elderly to levels of middle-aged controls, following 6 months of explosive resistance training. Thus, resistance training may lessen coactivation in persons with MS. However, neural adaptation may be blunted in persons with MS because of the pathophysiology of MS. Nevertheless, neural adaptations may improve physical function and postural control in persons with MS by increasing central activation of the muscle and maximizing force generation.

**Summary: Effect of resistance training on motor performance in MS**

Strength and power gains can be achieved in persons with MS following resistance training, however to what extent is unknown. Neural adaptation may impede negative changes in the nervous system due to MS by increasing motor unit discharge rates and reducing coactivation. Neural adaptations may also improve postural control in persons with MS, suggesting a cause and effect relationship between neural input and postural stability.
Figure 2.1.

The contribution of neural adaptation and muscle hypertrophy to strength gains changes over time during resistance training. Neural adaptation plays a greater role in strength gains early in resistance training (10 reps of dumbbell exercises at 66% RM using elbow flexors, 2x per day, 3x per week for 8 weeks), whereas muscle hypertrophy plays a greater role later in resistance training in young adults. Adapted from Moritani and DeVries (69).
CHAPTER 3
PROPOSED METHODS FOR STUDY 1

Participants

Persons with MS and age- and gender-matched non-MS controls will be recruited from the local community. The inclusion and exclusion criteria are presented in Table 3.1. Group sizes (n=12 in each group) were estimated from various measures of interest (see Table 3.2). Due to the lack of information about passive torque in persons with MS, 14 participants in each group will be studied. This study will be part of a larger study, funded by the National Multiple Sclerosis Society RG-3974.

Experimental Design

All participants will be screened over the phone prior to their first visit. Visits 1 and 2 will be conducted in the Muscle Physiology Laboratory. During Visit 1, participants will read and sign the informed consent document prior to their participation in the study. The following forms will also be completed by the participant: self-reported EDSS (14); Fatigue Severity Scale (FSS; (60)), Modified Fatigue Impact Scale (MFIS), Spasticity Scale, Medical History Questionnaire, Physical Activity Readiness Questionnaire, and Magnetic Resonance Safety Questionnaire. Height, mass, and physical function\textsuperscript{41} will be measured. Familiarization to Biodex procedures will also take place. Prior to leaving the lab, participants will be given an accelerometer (GT1M, Actigraph Inc., Pensacola, FL) to wear around their waist for 7 days during waking hours. An activity log will also be provided for participants to record their daily activities. Accelerometry will be used to match physical activity

\textsuperscript{41}physical function – measures include 10 s rapid foot-tapping, 10m timed walk at brisk and usual speeds, timed up-and-go test, timed chair rises (x5)
levels between MS and non-MS groups, to prevent potential confounding results due to differences in physical activity.

In Visit 2, participants will perform the Passive Torque, Isometric Contraction, Dynamic Contraction, and Electrical Stimulation Protocols. In Visit 3, participants will perform the Intramuscular Electromyography Protocol in the Exercise Neuroscience Laboratory. Visits 2 and 3 will be separated by 7 days to ensure adequate rest and to avoid muscular fatigue. The order of which leg is studied first will be randomized and balanced across groups. To minimize symptomatic fatigue in persons with MS, the laboratories will be air-conditioned. Visit 4 will take place in the Magnetic Resonance Imaging (MRI) Center at Cooley Dickinson Hospital, where the participant’s thigh muscles will be imaged. Table 3.3 summarizes the participant’s schedule for Study 1.

**Biodex Isokinetic Dynamometer**

Following a 3 minute warm up on a recumbent cycle ergometer (Schwinn 210p; at no resistance), participants will be seated on the Biodex dynamometer (Biodex Medical, Shirley, NY, U.S.A.) with the hip angle set at ~90°. The knee joint will be aligned with the axis of the dynamometer arm. Velcro straps will be used to secure the leg to the dynamometer arm. Shoulder, waist, and thigh straps will be used to stabilize the body and leg. Although the KE are the primary muscle groups of interest in this study, the knee flexors (KF) will also be tested for normalization of EMG responses. For isometric contractions, the knee angle will be fixed at 90° flexion for knee extension and knee flexion. In addition, the knee will be fixed at the optimal angle for knee extension and knee flexion (80° and 40° flexion, respectively) to measure maximal

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42 90° knee flexion – relative to full extension (0 degrees)
force production and maximal EMG activity. For passive and voluntary dynamic knee extension, the total range of motion (ROM) will be 70°, starting at 90° flexion. Verbal encouragement will be provided for all contractions. Torque, velocity, position, and EMG signals will be sampled at 1000 Hz using a customized data acquisition program in MATLAB software (MathWorks Inc., Natick, MA, U.S.A.). Two surface, bipolar electromyography (EMG) electrodes will be taped onto the skin above the vastus lateralis and semimembranosus muscles at sites recommended by Cram et al. (24). These muscles were chosen to minimize any potential cross-talk that may occur during muscle activity.

**Passive Torque Protocol**

Passive torque (N·m) will be measured in each leg for the following velocities obtained in random order and blocked by group: 10, 30, 60, 90, 120, 150, 180, 210, 240, 270, and 300 °·s\(^{-1}\). Two continuous cycles of knee extension and flexion will be recorded at each velocity with 5 s rest between directions. The passive torque obtained at 10 °·s\(^{-1}\) will serve as “baseline” when comparing torques at other velocities. This comparison will detect any increments in passive torque that occur at higher velocities due to greater resistance. Torque, position, and velocity data will be recorded. After correcting for torques due to the moment of inertia, peak torque over the range of motion will serve as the index of spasticity. Passive-to-voluntary torque ratio during knee extension will be calculated at each velocity and will be a measure of the effect of spasticity in the KF on voluntary torque production in the KE.
Isometric Contraction Protocol

Participants will perform 3 maximal voluntary isometric contractions (MVIC, N·m; 3-4 s duration) of the KE and KF of each leg, with 2 minutes of rest between contractions. If the highest MVIC trials are not within 10% of one another, then additional trials\(^ {43}\) will be performed.

Dynamic Contraction Protocol

Voluntary torque production of the KE will be measured in each leg. Two consecutive (2-3 s rest between contractions) maximal voluntary contractions will be performed at each of the following velocities: 30, 60, 90, 120, 150, 180, 210, 240, 270, and 300 °·s\(^{-1}\). The order of the velocities will be same as the Passive Torque Protocol. Participants will be instructed to “contract as hard and fast as possible” prior to each contraction. Further encouragement will be given during the contraction. Once the end of the ROM is achieved after each contraction, the leg will be moved passively back to the starting position at a velocity of 60 °·s\(^{-1}\). Participants will have 2 min of rest between velocities.

Electrical Stimulation Protocol

The knee angle will be set at 90° flexion. Before placing the surface electrodes over the KE, the skin will be abraded and cleansed with abrasive cream and alcohol, to improve the signal-to-noise ratio. A constant current stimulator (model DS7A, Digitimer, Hertfordshire, UK) and two 3” x 5” adhesive pad electrodes, placed at proximal and distal ends of the KE, will be used to apply a 80 Hz tetanus. The stimulation intensity will be determined by incrementing the current until 50% of MVIC

\(^{43}\) additional trials – total of 6 trials
is achieved. Then, 3 tetanic trials will be performed with 2 min of rest between trials. This protocol will be conducted on KE of both legs.

**Intramuscular EMG Protocol**

Motor unit firing rates will be collected in the Exercise Neuroscience Laboratory. Participants will be seated upright with hip and knee angle fixed at ~90°. A heavy-duty Velcro strap will be wrapped around the waist to stabilize the body. A Velcro strap will be used to secure the ankle to a force transducer (Interface SM-250, Scottsdale, AZ).

Participants will perform 3 MVICs of KE, separated by 2 min, with visual feedback of their force production on a computer screen. If the MVICs are not within 10% of each other, additional MVICs will be performed. Then, participants will briefly practice achieving 50% MVIC.

Once peak MVIC is determined, the skin over the knee cap and belly of the vastus lateralis will be cleansed with alcohol. A stainless steel ground electrode will be taped to the knee cap. Then, a sterilized, four-wire needle electrode will be inserted into the belly of the vastus lateralis to record intramuscular EMG activity. This electrode consists of a 27-gauge stainless steel cannula, which houses a square array of four 50 μm-diameter platinum-iridium wires, and provides three recording channels of motor unit activity. The electrodes will be connected to a Dantec Clinical Electromyograph (Dantec Counterpoint, Dantec Electronik Medicinsk, Skovlunde, Denmark) where the intramuscular EMG signals will be displayed on a digital oscilloscope. Analog signals from the EMG electrodes will be bandpass filtered (1-10 kHz) and amplified (mV/D) in
the Dantec Clinical Electromyograph. Signals from the Dantec and force transducer will be acquired at 25.6 kHz.

After ensuring the subject’s comfort, the subject will be asked to contract their KE at 10 to 30% of MVIC to verify good placement of the needle electrode by viewing all 3 channels of motor unit action potentials. If required, a slight adjustment to the location of the electrode will be made to obtain clear recordings of motor unit action potentials.

Prior to contraction, participants will be instructed “to contract as hard as they can” until they are cued to relax. Participants will perform a 5 s MVIC with 2 min of rest between trials. Slight adjustments of the electrode will be performed between trials to obtain clear recordings of motor unit action potentials, as well as to sample different motor units. After achieving 3 good trials of clear recordings, participants will be asked to perform 50% MVIC (using visual feedback of their force production) for 8-10 s, with 2 minutes of rest between trials. Again, small manipulations of the needle electrode will be made between recordings, and 3 good trials will be achieved before ending the protocol.

**Magnetic Resonance Imaging (MRI) Protocol**

Participants will visit the MRI Center at Cooley Dickinson Hospital. All participants will be screened with a Magnetic Resonance Safety Questionnaire prior to entry into the magnet room. Proton MRI will be performed using a 1.5 Tesla whole-body system (General Electric Company). Participants will be supine on a bed, and a phase-array coil will be wrapped around the thigh. The bed will then be moved into the bore of the magnet so that the mid-thigh is positioned at the isocenter. Forty-six T1-
weighted serial transverse images will be obtained. The following parameters will be used in acquiring serial images: 256 x 256 matrix, field of view of 300mm, 2 averages, and slice thickness of 6mm with no gaps. Participants will have both legs imaged.

**Data Processing**

All participants will be coded by the investigator prior to data collection. Following each participant’s completion of the study, identifiable paperwork will be removed from the participant folder. Unless specified otherwise, all data processing will be conducted using custom-designed programs in MATLAB.

**Strength and Power**

All torque data will be corrected for the effects of gravity to account for the weight of the limb and apparatus. The highest MVIC will be used for maximal strength and to calculate specific strength (N·m·cm⁻²). Power (W) will be calculated as the product of torque and velocity. Peak power will be determined by taking the highest power calculated from all velocities. Torque and power pilot data from a non-MS male participant are presented in Figure 3.1.

**Neuromuscular Drive**

Acquired signals of motor unit action potentials will be up-sampled to 51.2 kHz. Simultaneously acquired force data will be down-sampled to 50 Hz. Individual motor unit action potentials will be identified using customized spike recognition algorithm software, which is an automatic spike detection system that makes use of the discharge history and template-matching for identification. Following auto-identification of motor units, manual identification will be performed to resolve superpositioned motor units and to correct for mis-identified motor units. The interpulse interval (s) between
consecutive firings of a given motor unit will be determined and averaged during the peak plateau of a MVIC. The firing rate (pulses per second, pps) of a given motor unit will be calculated by taking the inverse of the interpulse interval. The mean firing rates of all motor units per contraction will be calculated\textsuperscript{44}. The maximum and mean firing rates during 50% and 100% MVIC for each participant will be determined. Pilot data from a non-MS male participant are presented in Figure 3.2.

Specific force will be calculated by normalizing MVIC with muscle cross-sectional area (mCSA), which will be determined by MRI. For each cross-sectional slice, the signal intensity thresholds will be determined to discriminate contractile from non-contractile tissue. The 3 largest consecutive knee extensor mCSAs will be analyzed twice by manually outlining the knee extensors, and then, averaged. As another secondary measure of neuromuscular drive, we will use the ratio of voluntary-to-stimulated rate of force development.

**Contractile Function**

The rate of force development during a 50 Hz tetanus will be expressed as percent of peak force per ms and will be a measure of contractile speed. In addition, the velocity that results in 50% of isometric force will be used to determine changes in contractile function, represented by shifts in the voluntary torque-velocity relationship in persons with MS compared to non-MS controls.

**Spasticity and Coactivation of Spastic Antagonist Muscles**

Peak passive torque (N m) will be determined at each velocity following moment of inertia correction. The lowest velocity that produces passive torque and

\textsuperscript{44} firing rates of all motor units … will be calculated – doublets and interpulse interval $> 200$ ms will not be included in the calculation of motor unit firing rates
EMG activity together will serve as the spasticity threshold. A linear envelope will be applied to the surface EMG data and the area of linear envelope will be used as a measure of muscle activity. The ratio of normalized KF and KE EMG activity will be used as a measure of coactivation. Pilot data of torque and surface EMG during voluntary dynamic knee extension from a non-MS male participant are presented in Figure 3.3.

**Statistical Analyses**

All statistical analyses will be performed using Statistical Analysis Software (SAS Institute Inc., version 8.0, Cary, NC). To characterize our participants, unpaired *t*-tests will be used to detect differences between persons with MS and non-MS controls in: age, height, mass, FSS, MFIS, spasticity scale, foot-tap counts, walk times, timed up-and-go test, timed chair rises, MVIC, peak power, specific strength, spasticity threshold, velocities at 50% MVIC, and total accelerometer counts. A 2-way repeated measures analysis of variance (rmANOVA; group x velocity) will be used to detect differences in passive torque between groups over the range of velocities.

For *Hypotheses 1.1 to 1.3*, an unpaired *t*-test will be used to detect group differences in muscle cross-sectional area, motor unit firing rates during 50% and 100% MVIC, ratio of voluntary-to-stimulated rate of force development, and stimulated rate of force development. For *Hypothesis 1.4*, a 2-way rmANOVA (group x velocity) will be tested on passive-to-voluntary torque ratio to detect differences across groups over a range of velocities. In the case of significant interactions, post hoc analyses (Tukey’s) will be performed to determine where differences occur. To explore which mechanisms may explain muscle strength (i.e., mCSA, motor unit firing rates) and power (i.e.,
mCSA, motor unit firing rates, passive-to-voluntary torque ratio, contractile properties) decrements in persons with MS, multiple linear regression analyses will be performed.

The level of significance will be set at $p \leq 0.05$. Data will be expressed as mean ± SD. Precise p-values and the 95% confidence interval for differences between groups will be reported, where appropriate.
Table 3.1.

Inclusion and exclusion criteria.

<table>
<thead>
<tr>
<th>Inclusion criteria for all persons with MS</th>
<th>Inclusion criteria for all participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Clinically verified MS</td>
<td>- Are between the ages of 21 and 60 years</td>
</tr>
<tr>
<td>- Self-reported Expanded Disability Status Score (EDSS) between 2 and 6</td>
<td>- Are sedentary to recreationally-active</td>
</tr>
<tr>
<td>- No exacerbations in the past 6 months</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion criteria for all participants</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Have a metabolic, non-MS neurologic, cardiovascular, or other disease</td>
<td></td>
</tr>
<tr>
<td>- Taking any medications (other than for MS) that may affect muscle function</td>
<td></td>
</tr>
<tr>
<td>- Are pregnant</td>
<td></td>
</tr>
<tr>
<td>- Have a cognitive impairment or a mental disorder that precludes following protocol instructions</td>
<td></td>
</tr>
<tr>
<td>- Have arthritis in the lower extremities</td>
<td></td>
</tr>
<tr>
<td>- Have a history of dyspnea, cramping, or light-headedness during exercise</td>
<td></td>
</tr>
<tr>
<td>- Are currently smokers or stopped smoking within the past 6 months</td>
<td></td>
</tr>
</tbody>
</table>
Table 3.2.
Sample size estimates were calculated using unpaired t-tests (power set at 80% and significance level set at 0.05) on variables of interest in Study 1. SD = standard deviation. KE = knee extensors. VL = vastus lateralis. DF = dorsiflexors. MVIC = maximal voluntary isometric contraction. AP COP = center of pressure in the anterior-posterior direction. MUFR = motor unit firing rates. mCSA = muscle cross-sectional area. RFD = rate of force development. $T_{1/2}$ = half-time of force relaxation.

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Variable</th>
<th>Mean of Non-MS</th>
<th>Mean of MS</th>
<th>Mean of other</th>
<th>SD</th>
<th>Sample size estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>(121)</td>
<td>KE MVIC (N·m)</td>
<td>156</td>
<td>92</td>
<td>38</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>(21)</td>
<td>KE power (W)</td>
<td>206</td>
<td>155</td>
<td>42</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AP COP variability (mm)</td>
<td>4.33</td>
<td>7.52</td>
<td>1.79</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>(37)</td>
<td>Passive KE torque at 120°/s (N·m)</td>
<td>27.9</td>
<td>38.8 (stroke)</td>
<td>8.4</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>(106)</td>
<td>VL MUFR (pps)</td>
<td>23.8</td>
<td>13.1</td>
<td>2.6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>(57)</td>
<td>DF mCSA (cm²)</td>
<td>11.1</td>
<td>7.8</td>
<td>1.2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>(113)</td>
<td>RFD (% peak force·ms⁻¹)</td>
<td>1017</td>
<td>846</td>
<td>50</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>
Table 3.3.

Summary of participant’s schedule for Study 1.

<table>
<thead>
<tr>
<th>Visit</th>
<th>Location</th>
<th>Description</th>
<th>Approximate Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Muscle Physiology Lab – UMass</td>
<td>Paperwork, physical function assessments, Biodex Familiarization, accelerometry</td>
<td>2 hrs</td>
</tr>
<tr>
<td>2</td>
<td>Muscle Physiology Lab – UMass</td>
<td>Contraction and Electrical Stimulation protocols</td>
<td>2.5 hrs</td>
</tr>
<tr>
<td>3</td>
<td>Exercise Neuroscience Lab – UMass</td>
<td>Intramuscular Electromyography</td>
<td>1.5 hrs</td>
</tr>
<tr>
<td>4</td>
<td>MRI Center – Cooley Dickinson Hospital</td>
<td>MRI of thigh muscles</td>
<td>1.25 hrs</td>
</tr>
</tbody>
</table>
Figure 3.1.

Torque (top) and power (bottom) data from a non-MS male participant across a range of velocities.

[Graph showing torque (N.m) and power (W) vs. velocity (deg/s) with data points for passive, active, and passive:torque.]
Figure 3.2.

Pilot data of the mean and maximum motor unit firing rates at 50% and 100% MVIC from a non-MS male participant.
Figure 3.3.

Torque and surface EMG of the VL and SM of 3 consecutive dynamic contractions at 120 °·s⁻¹ (top) from a non-MS male participant. VL = vastus lateralis. SM = semimembranosus.
CHAPTER 4

PROPOSED METHODS FOR STUDY 2

Participants

Sample size estimates were determined from DeBolt et al. (31) and Christie and Kamen (19), which suggested 13 and 10 participants in each group, respectively, to detect differences in muscle power and motor unit firing rates pre-to-post training at 80% statistical power. Therefore, 10 participants with and 10 without MS will be recruited from Study 1 and from the local community. All participants will undergo resistance training in the Muscle Physiology Laboratory. Study 2 will also be a part of a larger study, funded by the National Multiple Sclerosis Society RG-3974.

Experimental Design

Table 4.1 summarizes the study timeline for each participant. Participants will come to the laboratories (Muscle Physiology and Exercise Neuroscience Labs) for a total of 10 visits: a familiarization visit, 2 pre-training visits, 6 resistance training sessions and 1 post-training visit. With the exception of the intramuscular EMG protocol, which will be conducted in the Exercise Neuroscience Lab, all procedures will be performed in the Muscle Physiology Lab.

During Visit 1, participants will read and sign the informed consent document prior to their participation in the study. Once consent is given, all participants will fill out the Medical History questionnaire, Physical Activity Readiness questionnaire, Fatigue Severity Scale (FSS), and Modified Fatigue Impact Scale (MFIS). Persons with MS will also fill out the self-reported EDSS. Height, body mass, and blood pressure will be measured. To evaluate physical function, participants will perform 10 s of rapid
foot-tapping, 10 m timed walk at a brisk and usual paces, timed up-and-go test (8 ft), and 5 timed chair rises. At the end of Visit 1, participants will become familiar with the isometric and dynamic contraction protocols on the Biodex isokinetic dynamometer (Biodex Medical, Shirley, NY, U.S.A.) on both legs, which will determine the weaker leg that will be used for pre- and post-training measure of intramuscular EMG.

Visit 2 will involve isometric and dynamic contractions with bipolar EMG electrodes taped over the vastus lateralis and semimembranosus muscles. Visit 3 will consist of postural control measures and intramuscular EMG. Resistance training will begin the day after the pre-training measures (Visits 4-9). The first set of maximal repetitions on the last training visit (Visit 9) will be replaced with the dynamic contraction protocol, to re-assess the load-power relationship. The day following the last training session (Visit 10), postural control measures and intramuscular EMG will be re-assessed. In addition, participants will perform the same physical function measures as in Visit 1, to determine whether increases in strength and power are associated with improved physical function. Visits 1 and 2 will be separated by 3 to 7 days to ensure adequate rest prior to pre-training measures.

**Biodex Isokinetic Dynamometer**

Following a 3-min warm-up on a recumbent cycle ergometer with no resistance (Schwinn 210p, Nautilus, Inc., Vancouver, WA), participants will be seated on the Biodex dynamometer with the hip angle set at ~90°. The knee joint will be aligned with the axis of the dynamometer arm, and Velcro straps will be used to secure the weaker leg. Shoulder, waist, and thigh straps will also be used to stabilize the body and leg. The procedures for isometric contractions of the KE and KF, dynamic contractions of
the KE, and surface EMG electrode placement over the vastus lateralis and
semimembranosus muscles will be the same as in Study 1. Verbal encouragement and
visual force feedback during contractions will be provided to all participants. Analog
signals from the Biodex dynamometer (torque, velocity, position) and EMG electrodes
(Delsys, Boston, MA) will be converted to digital signals (National Instruments
Corporation, Austin, TX) and sampled simultaneously at 2500 Hz using a customized
data acquisition program in MATLAB software (MathWorks Inc., Natick, MA, U.S.A.).

**Isometric Contraction Protocol**

Participants will perform 3 MVICs (N·m; 3-4 s duration) of the KE and KF,
with 2 min rest between contractions. If the 2 highest MVIC trials within each muscle
group are not within 10% of one another, then additional trials (up to 6 MVICs) will be
performed.

**Dynamic Contraction Protocol**

Voluntary torque production of the KE will be measured in the non-dominant
leg. Two consecutive (2-3 s rest between contractions) maximal voluntary dynamic
contractions (MVDC) will be performed at each of the following loads: 20, 30, 40, 50,
60, and 70 % MVIC. These velocities were chosen to evaluate peak power from the
load-power relationship for each participant. The order of the velocities will be
randomized across participants and balanced across groups. Once the end of the ROM
is achieved, the leg will be moved passively back to the starting position. Participants
will have 2 min of rest between velocities. The optimal load at which peak power is
produced will be used as the intensity for resistance training.
Postural Control Protocol

Retroreflective markers will be placed on the participant’s head, trunk, pelvis, arms and legs for the calculation of whole-body center of mass in 3 dimensions. Marker triads will also be placed over the upper arms, thighs and calves (Figure 4.1). Two adjacent force plates (Advanced Mechanical Technology Inc., Watertown, MA) will be used to record ground reaction forces. Participants will stand with their feet hip-width apart and each foot placed on its own force plate. Participants will perform 2 trials of quiet stances, each lasting for 30 s. Data will be acquired from a camera system (Proreflex MCU 240, Qualysis, Gothenburg, Sweden) using Qualisys Track Manager (Qualysis Medical AB, Gothenburg, Sweden). The analog signals from the camera and force plates will be sampled at 240 Hz.

Intramuscular EMG Protocol

Maximal motor unit firing rates will be collected in the Exercise Neuroscience Lab. The procedures will be the same as in Study 1. Only the weaker leg will be studied.

Resistance Training Protocol

Participants will come to the Muscle Physiology Lab for ~30 min, 3 times per week for 2 weeks. Both legs will be trained to examine how changes in strength and power affect physical function after training. At the start of each session, participants will warm up on a recumbent cycle ergometer for 3 minutes. Then, participants will be seated on the Biodex dynamometer and will perform 3 MVICs of the KE, with 2 min of rest between trials. This procedure will allow us to track strength gains during the course of the training protocol. The intensity of resistance training will be set at an
optimal load (% MVIC) at which peak power is produced from the load-power relationship. Participants will perform 3 sets of 10 maximal repetitions at the optimal load, with 5 min of rest between sets. Participants will be instructed to contract their muscles rapidly and forcefully against the load imposed by the dynamometer. Verbal encouragement and torque feedback (light diode box) will be given to each participant at each training session. Torque, position, and velocity will be recorded during the training sessions.

**Data Processing**

All data processing for torque, power, co-activation, motor unit firing rates will be the same as in Study 1. Visual 3D™ (C-Motion, Inc., Rockville, MD) will be used to compute the center of pressure (COP) for each foot from ground reaction forces, as well as whole-body center of mass from marker coordinates. The net center of pressure represents the whole body center of pressure, calculated as:

\[
CoP_{net} = \left( CoP_{left} \cdot \frac{Fz_{left}}{Fz_{left} + Fz_{right}} \right) + \left( CoP_{right} \cdot \frac{Fz_{right}}{Fz_{left} + Fz_{right}} \right) \quad \text{equation 1}
\]

where \(Fz\) is the ground reaction force, and left and right refers to the left or right force plate (130). The center of pressure variability will be the standard deviation of the net center of pressure over a time series in the AP and ML directions.

Time-to-contact (TtC) of the center of mass in the AP direction will be calculated by taking the average of the instantaneous distance and velocity of the whole body center of mass with respect to the stability boundary over time:

\[
TtC(i) = \frac{d(i)}{V_{COM}(i)} \quad \text{equation 2}
\]
where \( d(i) \) is the instantaneous distance from the whole body center of mass to the AP stability boundary (defined by the perimeter of the feet) and \( V_{\text{COM}}(i) \) is the instantaneous velocity of the center of mass in the AP direction \((125) \) (Figure 4.2). In quiet stance, the center of mass would not normally cross the stability boundary. Therefore, \( TtC \) is the predicted time it would take for the center of mass to reach the stability boundary based on its current position and velocity. Figure 4.3 presents the time series of \( TtC \) from a non-MS male participant.

**Statistical Analyses**

All analyses will be performed using Statistical Analysis Software (SAS Institute Inc., version 8.0, Cary, NC). Unpaired \( t \)-tests will be used to detect differences in group characteristics (age, height, body mass, FSS, MFIS, and spasticity scale). To test the hypotheses, 2-way repeated measures ANOVA (group x time) will be used to examine the changes from pre- to post-resistance training in: MVIC, peak power, maximal motor unit firing rates, co-activation, net COP variability, \( TtC \), and physical function (foot-tap counts, brisk and usual pace walk times, timed up-and-go test, and timed chair rises). If significant interactions are present, post hoc analyses (Tukey’s) will be used to determine where significant differences occur. Linear regression analyses will be performed to determine associations between muscle strength, power, physical function and postural control.

The level of significance will be set at \( P \leq 0.05 \). Data will be expressed as mean \( \pm \) SD. Precise p-values and 95% confidence intervals for differences between groups will be reported, where appropriate.
Table 4.1.

Summary of participant’s schedule for Study 2. Baseline measures will take place in Visits 2-3, and post-training testing will take place in Visits 10. During Visit 9, the first set will be replaced with the dynamic contraction protocol with surface EMG, to reassess load-power relationship.

<table>
<thead>
<tr>
<th>Visit</th>
<th>Location</th>
<th>Description</th>
<th>Approximate Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Muscle Physiology Lab</td>
<td>Paperwork, physical function assessments, Biodex familiarization</td>
<td>1.5 hrs</td>
</tr>
<tr>
<td>2</td>
<td>Muscle Physiology Lab</td>
<td>Isometric and Dynamic Contraction protocols plus surface EMG on both legs</td>
<td>2.5 hrs</td>
</tr>
<tr>
<td>3</td>
<td>Motor Control Lab</td>
<td>Postural Control protocol</td>
<td>1.25 hrs</td>
</tr>
<tr>
<td>3</td>
<td>Exercise Neuroscience Lab</td>
<td>Intramuscular EMG of vastus lateralis on weaker leg</td>
<td>1.25 hr</td>
</tr>
</tbody>
</table>

Visits 4-9
2 weeks of resistance training on both legs
3x per week
3 sets of 10 maximal repetitions at optimal load

| 10    | Motor Control Lab         | Postural Control protocol                                                   | 1.25 hrs             |
| 10    | Exercise Neuroscience Lab | Intramuscular EMG of vastus lateralis on weaker leg                         | 1.25 hr              |
Figure 4.1.

For postural control measures, retroreflective markers will be placed on the head, trunk, pelvis, arms, and legs for calculation of whole body center of mass.
Figure 4.2.

Adapted from van Wegen et al. (125), this is a pictorial representation of the time-to-contact (TtC) measure. Time-to-contact (TtC) of the center of mass in the AP direction will be calculated by taking the average of the instantaneous distance ($d$) and velocity ($v$) of the whole body center of mass (COM) with respect to the stability boundary (solid line around feet) over time.
Figure 4.3.

Time series of TtC during 60 s of quiet stance from a non-MS male participant.
CHAPTER 5
MECHANISMS OF MUSCLE WEAKNESS IN PERSONS WITH MULTIPLE SCLEROSIS

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Running title: Muscle weakness in MS
MECHANISMS OF MUSCLE WEAKNESS IN PERSONS WITH MULTIPLE SCLEROSIS

Abstract

The aim of this study was to identify the key contributors to knee extensor muscle weakness in persons with MS. Lower peak isometric torque (Nm) and power (W) were shown in MS (n=14; 12 females, 2 males), compared with age-matched control (n=14; 11 females, 3 males). Smaller fat-free muscle cross-sectional area (magnetic resonance imaging, cm²; p=0.04) and lower maximal motor unit discharge rates (p=0.04) in the vastus lateralis were observed in MS compared with control. Specific strength (Nm·cm⁻²; p=0.48) was not different across groups, but specific power (W·cm⁻²; p=0.05) was lower in MS. These results suggest that smaller muscle size and lower motor unit discharge rates explain much of the weakness in persons with MS. Because muscle size accounted for differences in isometric strength, but not entirely for differences in power, the mechanisms of weakness in MS appear to be contraction-mode specific, and include both anatomical and neural mechanisms.
**Introduction**

A common symptom of multiple sclerosis (MS), an auto-immune disease of the central nervous system, is muscle weakness. Lower isometric (18; 80; 82; 83; 111; 113) and dynamic (3; 16; 21; 63; 99; 121) torque have been shown in persons with MS compared with non-MS controls. Weakness is particularly evident in the knee extensor muscles (3; 18; 21; 63; 99; 111; 121). Despite numerous studies on isometric strength and dynamic power in persons with MS, the mechanisms of MS-related changes in force production remain unclear.

Muscle weakness in MS may be a direct consequence of changes in the central nervous system due to demyelination, a defining feature in MS that compromises the rapid and complete transmission of action potentials to effector organs, such as skeletal muscle. Investigators have reported central activation failure in persons with MS in the ankle dorsiflexor (82; 113) and knee extensor (28) muscles. Lower maximal motor unit discharge rates have been shown in a small group of 4 individuals with MS compared with controls during a MVIC (106). In other neuromuscular disease patients, lower rate of force development, normalized to the rate of force development during a stimulated contraction, was observed compared with controls (59), suggesting alterations in neural drive during voluntary force production.

Spasticity, another common symptom in MS, may contribute to power deficits in this population. Spasticity is characterized as “a velocity-dependent resistance to passive stretch by the antagonist muscle due to the hyperexcitability of the stretch reflex” (64). That is, co-activation of antagonist muscles due to spasticity may slow contraction velocity and lower power production of agonist muscles, particularly during
high contraction velocities. Clinically, spasticity is assessed using the Ashworth or Modified Ashworth Scales (11). Numerous investigators have used biomechanical and electrophysiological techniques to quantify spasticity in stroke (4; 98), spinal cord injury (37; 51; 76; 96; 100), and MS (8; 88; 90). Torque resistance to passive limb (i.e., passive torque) movement is one measure of spasticity that is obtained using a dynamometer. Nuyens et al. (90) observed higher passive torque during knee extension and knee flexion in persons with MS compared with controls. Spasticity has not been measured in the context of its potential effect on muscle weakness in MS. Thus, it is not known whether the degree of spasticity in an antagonist muscle may explain a portion of lower torque production of the agonist muscle during dynamic contractions in persons with MS.

Lower fat-free muscle cross-sectional area is observed in persons with MS in the ankle dorsiflexor muscles (57). In addition, studies have shown lower single fiber cross-sectional area of ankle dorsiflexor (57) and vastus lateralis (44) muscles in persons with MS compared with controls. Together, these results suggest that smaller muscle size is a contributor to muscle weakness in MS. Investigators have reported a modest decline (82) or no difference (57) in specific strength (force normalized to muscle size) of the ankle dorsiflexor muscles in individuals with MS compared with controls, indicating that muscle quality may or may not be reduced. To date, no studies have examined specific strength and specific power in the knee extensor muscles in persons with MS.

Alterations in contractile function may limit power (a product of contraction velocity and torque production), as a slower rate of force development may impede
contraction velocity. Lower rates of force development during a stimulated contraction are observed in the ankle dorsiflexor muscles in persons with MS compared with controls (113). However, others have shown no difference between persons with MS and controls in the maximal rate of force development in the knee extensor muscles (28; 30). Thus, it is not clear whether lower power may be partially explained by slower contractile properties.

Indeed, there are a number of potential mechanisms that could contribute to muscle weakness in persons with MS. The extent to which these mechanisms influence overall strength and power in persons with MS is not clear. Further, muscle weakness in MS has been associated with lower physical function (21; 121) and symptomatic fatigue (21), another significant symptom of MS. These relationships suggest that muscle weakness has a negative impact on activities of daily living and overall quality of life in persons with MS.

The aim of this study was to systematically determine the mechanisms of diminished isometric strength and dynamic power in the knee extensor (KE) muscles of persons with MS. We hypothesized that, compared with controls, persons with MS would have 1) lower peak isometric torque and power, 2) lower maximal motor unit discharge rates in the vastus lateralis muscle, 3) higher passive torque in the knee flexors (KF) and higher percentage of KF passive-to-KE voluntary torque during high-velocity (>120 °·s⁻¹) contractions, 4) slower voluntary rate of force development (RFD), 5) lower fat-free KE muscle cross-sectional area, 6) lower specific strength and lower specific power, and 7) slower stimulated RFD. In addition, isometric strength and power associations with key mechanisms of weakness were explored. Associations
between isometric strength, power, physical function and symptomatic fatigue were also explored.

**Methods**

**Study Design**

Participants came in for a total of 4 visits, each separated by 3 to 7 days. Detailed information for each measure is described in the following sections. Briefly, *Visits 1* and 2 were conducted in the Muscle Physiology Laboratory. At *Visit 1*, signed informed consent, participant characteristics and measures of symptomatic fatigue were collected; and familiarization with the Biodex dynamometer (Biodex Medical, Shirley, NY, U.S.A.) procedures was performed. Isometric strength was measured in each leg to determine which was weaker. At the end of *Visit 1*, participants were issued an accelerometer and instructed in its use. At *Visit 2*, physical function, muscle strength, power, spasticity and contractile function were measured on the weaker leg. At *Visit 3*, motor unit discharge rates of the vastus lateralis of the weaker leg was measured in the Exercise Neuroscience Laboratory. At *Visit 4*, magnetic resonance imaging (MRI) of the weaker thigh was conducted, in the MRI Center of Cooley Dickinson Hospital.

**Group Characteristics**

Fourteen persons with MS (12 females, 2 males) and 14 age-matched individuals without MS (11 females, 3 males) gave signed informed consent, as approved by the Institutional Review Board at the University of Massachusetts, Amherst. Participants were recruited from the university and surrounding communities, as well as through the Central New England Chapter of the National MS Society.
Participants completed the Spasticity Scale (107), a medical history form, the Physical Activity Readiness Questionnaire (119), and a magnetic resonance safety questionnaire.

Persons with MS were moderately impaired, as determined by their self-reported Expanded Disability Status Scale (sEDSS (14)) score of 4.7 ± 1.1 (mean ± SD, range 3-6). Of the 14 persons with MS, 13 individuals had relapsing-remitting and 1 individual had the primary-progressive subtype. Medications taken by participants with MS included [number of individuals]: immuno-modulators [13], anti-depressants [5], analeptics [4], bladder-control medications [3], muscle relaxants [3], and anti-hypertensives [2] (see Appendix B), and vitamin D supplements [5]. Of the participants with MS, 4 indicated having no symptoms of spasticity, 6 had some problems with spasticity that did not interfere with their activities, 2 had spasticity that forced them to change some of their activities about once a week, and 2 had problems with spasticity that forced them to modify their daily activities, based on the Spasticity Scale by Rizzo et al. (107). Participants with MS were excluded if they had an exacerbation within the previous 6 months.

All participants were healthy (other than MS-related symptoms), between the ages of 30 and 60 years, had no cardiovascular, neurological or neuromuscular disease (other than MS), were free from orthopedic injury in the legs, and were ambulatory. Sedentary to recreationally-active participants were recruited for both study groups to minimize differences in physical activity level. Five of the 14 controls were taking the following medications [number of individuals]: birth control [2], levothyroxine [2], and prilosec [1].
Anthropometrics. Height (m) and mass (kg) were recorded, and body mass index (BMI; kg·m$^{-2}$) was calculated. Leg length (knee joint axis to lateral malleolus of fibula) was measured on the tested leg, for calculation of the torque due to inertia (see Spasticity).

Symptomatic Fatigue. To characterize general fatigue and the impact of fatigue on quality of life, participants completed the Fatigue Severity Scale (FSS (60)) and the Modified Fatigue Impact Scale (MFIS; 21-items from Fatigue Impact Scale (38)), respectively. Scores for the 21-item MFIS were calculated as a sum of all item responses, whereas the 7-item FSS responses were averaged. Prior to the strength and power measures, participants were asked to draw a vertical line on the Visual Analog Fatigue Scale (VAFS (112)) to assess symptomatic fatigue at that point in time (i.e., “acute” fatigue). A ruler was used to score the VAFS, as each number (1 through 10) was separated by 1 centimeter. For all fatigue measures, a higher score reflects greater fatigue.

Physical Activity. To characterize and quantify habitual physical activity level, participants wore an accelerometer (GT1M, Actigraph Inc., Pensacola, FL) around their waist for 7 days, during all waking hours. An activity log was also provided for participants to record their daily activities and ensure appropriate wear time. Acceleration counts were acquired at a sampling frequency of 30 Hz and averaged in 30-s epochs. Non-representative days, indicated by self-report in the activity log or incomplete data collection, were not included in the analysis. Data from the accelerometer were downloaded using ActiLife software (Actigraph Inc., Pensacola, FL) and exported to a Microsoft Excel spreadsheet (Microsoft Corp., Redmond, WA).
Total daily accelerometer counts were averaged across a minimum of 5 days and used to represent the participant’s habitual physical activity level (counts·day$^{-1}·1000^{-1}$) (20; 65).

**Physical Function.** Physical function was measured to characterize the study groups. Participants were timed for their rapid completion of 5 consecutive chair rises, performed without the aid of their arms. Next, participants were asked to rapidly tap their foot for 10 s, one foot at a time, to assess neuromuscular function. Foot-tapping was performed twice and the highest count for each foot used for analysis. Mobility was assessed by having participants walk for 7.62 m (25 ft), first at a brisk and then at a usual pace. Each walk was performed twice and the fastest times were used for analysis.

**Isometric Strength and Power**

*Isometric Strength.* Participants were seated upright on the Biodex dynamometer. The upper body and thigh were stabilized with straps around the shoulder, waist and thigh. The knee joint was aligned with the axis of the dynamometer arm, and the leg was secured to the arm using a Velcro strap. The knee angle was fixed at 90° flexion. Although the KE was the primary muscle group of interest, knee flexors (KF) were also tested for muscle isometric strength. Torque, velocity, and position data were acquired at 2500 Hz using a customized data acquisition program in MATLAB software (Math Works Inc., Natick, MA, U.S.A.).

Three maximal voluntary isometric contractions (MVIC, Nm; 3-4 s duration) were obtained in the KE and KF, with 2 min of rest between contractions. Verbal encouragement and visual feedback of torque output (diode light box) were provided to
ensure a maximal effort by the participant. Maximal effort was confirmed when the highest 2 MVIC trials were within 10% of one another. Additional trials (no more than 6 trials in total) were performed if this criterion was not met. The highest peak torque was used as the primary outcome measure of muscle isometric strength.

*Power.* Following the isometric strength measures, the total range of motion was set at 70°, starting at 90° flexion from full extension. Participants performed maximal voluntary dynamic contractions at a range of velocities between 30 and 300 °·s⁻¹, at 30 °·s⁻¹ intervals. Participants performed 2 consecutive maximal voluntary dynamic contractions at each velocity, with 3-4 s rest between contractions. Two min of rest between each velocity was provided, to minimize muscle fatigue. The highest power generated at each velocity was recorded. Peak power was used as the primary outcome measure and the velocity at which peak power occurred was used for secondary analysis.

**Neural Factors**

*Motor Unit Discharge Rates.* Similar to the muscle testing protocol, participants were seated upright in a custom-built apparatus, with the knee angle fixed at ~90° flexion. The waist and thighs were secured to the chair by straps to stabilize the body. A Velcro strap was used to secure the ankle to a cuff that was connected to a force transducer (Interface SM-250, Scottsdale, AZ, U.S.A.). Participants performed 3 MVICs (4-5 s duration) of the KE, separated by 2 min of rest, to obtain baseline MVIC prior to insertion of the needle electrode. Verbal encouragement and visual feedback of torque output was provided on a computer screen using DasyLab Data Acquisition
software (MicroDAQ.com, Ltd., Contoocook, NH, U.S.A.). If the 2 highest MVIC trials were not within 10% of one another, additional MVIC trials were performed.

Once peak MVIC was determined, the skin over the patella and belly of the vastus lateralis muscle was cleansed with alcohol. A stainless steel ground electrode was taped over the patella. Then, a sterilized, four-wire needle electrode was inserted into the belly of the vastus lateralis, typically in the lower third of the thigh, to record intramuscular EMG activity. The electrode consisted of a 27-gauge stainless steel cannula that housed a square array of four 50 μm-diameter platinum-iridium wires, which provided 3 recording channels of motor unit activity (52). The ground and needle EMG electrodes were connected to a Dantec Clinical Electromyograph (Dantec Counterpoint, Dantec Electronik Medicinsk, Skovlunde, Denmark), where motor unit activity was displayed on a digital oscilloscope. Analog signals from the EMG electrode were amplified (200 or 500 μV·division⁻¹) and bandpass filtered (1-10 kHz) in the Dantec Clinical Electromyograph. Signals from the Dantec and force transducer were acquired and sampled at 25,600 Hz using DasyLab Data Acquisition software.

Following insertion of the needle electrode, participants performed 3 MVICs (4-5 s duration), with 2 min of rest between trials. Slight adjustments of the needle electrode were made between trials to obtain clear recordings of motor unit action potentials, as well as to sample different motor units. Clear recordings were characterized as crisp audio feedback and distinct motor unit action potentials displayed on the Dantec digital oscilloscope. Additional MVICs were performed if there were fewer than 3 MVICs with clear recordings.
Individual motor unit identification was performed using a customized spike recognition algorithm program, which automatically identified motor units based on discharge history and template-matching (52). Following auto-identification, motor unit identification was verified manually, and superpositioned and mis-identified motor units were corrected using a customized motor unit viewing and editing program. The interpulse interval (ms) between consecutive firings of a given motor unit was calculated, excluding doublets (≤ 10 ms) and long (≥ 200 ms) intervals. The discharge rate (pulses per second, pps) of a given motor unit was calculated by taking the inverse of the interpulse interval. The highest motor unit discharge rate (maxMUDR) was taken from an average of the 5 fastest interpulse intervals of a given motor unit. To obtain one value for each participant, all maxMUDR were averaged across motor units. As a secondary measure, the coefficient of variation of the mean motor unit firings was calculated for each motor unit to assess motor unit discharge variability. All coefficients of variation were averaged across motor units to obtain one value for each participant.

**Spasticity.** Spasticity was quantified using the passive mode on the Biodex dynamometer. Similar to the power set-up, the total range of motion was set at 70°, starting at 90° flexion from full extension. Participants were asked to remain relaxed while the leg was moved passively by the dynamometer. Torque, velocity and position were recorded during passive knee extensions were conducted at 10 °·s⁻¹ and from 30 to 300 °·s⁻¹, at 30 °·s⁻¹ increments (Figure 5.1A). Passive torque obtained at 10 °·s⁻¹ consisted of torque due to gravity and visco-elastic properties of the muscle, and was used to correct passive torque obtained at velocities ≥ 30 °·s⁻¹. Net passive resistive
torque and velocity were averaged across 20° and 50° extension from the starting position, for data collected at each velocity setting (Figure 5.1B). Because the dynamometer was unable to passively achieve velocities > 180 °·s⁻¹, a second-order polynomial fit was applied to the average passive torque and velocity data for the prescribed velocities between 30°·s⁻¹ and 300°·s⁻¹ (Figure 5.1C). Thus, for each participant, the equation obtained from the fit was used to estimate passive torque at all velocities achieved during the voluntary dynamic contractions (see Power section, above). Finally, the percentage of KF passive-to-KE voluntary torque was calculated for each participant, to examine the contribution of KF spasticity on KE voluntary torque production.

Voluntary Rate of Force Development. The maximal rate of force development during a maximal voluntary contraction was determined by the first derivative of the torque trace and expressed as the percentage of peak force per millisecond. To examine group differences in neural contributors to force production, the voluntary rate of force development was normalized to the stimulated rate of force development. See Contractile Function section, below, for more detail.

Muscle Factors

Contractile Function. To assess contractile function, 7.6 x 12.7 cm adhesive pad electrodes (VQ OrthoCare, Irvine, CA) were placed at the proximal and distal ends of the KE muscles. A stimulus train (80 Hz, 500 ms) was applied using a constant current stimulator (model DS7A, Digitimer, Hertfordshire, UK), in an isometric condition. The stimulation intensity was determined by incrementing the current until
50% of MVIC was achieved. The maximal rate of force development (RFD; % peak force·ms\(^{-1}\)) was determined from the first derivative of the torque trace.

**Muscle Size.** Magnetic resonance imaging (MRI) of the thigh was conducted using a 1.5 Tesla whole-body system (Siemens Medical Solutions USA, Inc., Malvern, PA) in the MRI Center at Cooley Dickinson Hospital. Participants lay supine on a bed with 2 phase-array coils placed over the thighs. The bed was automatically moved into the bore so that the mid-thigh was positioned in the isocenter of the magnet. Forty-six T1-weighted axial images were acquired in series, using the following parameters: 256 x 256 matrix, field of view of 300 mm, 2 averages, and slice thickness of 6 mm with no gaps.

All images were processed using a custom-written MATLAB program. Slices were visually inspected for quality and approximate location of the largest muscle cross-sectional area (mCSA). The largest slice and the 6 to 10 slices on either side of it were analyzed. For each slice, signal intensity thresholds were determined to discriminate contractile from non-contractile tissue (58), and the KE muscle group was outlined manually. From this analysis, ~7 of the largest, consecutive fat-free slices were identified, re-analyzed, and averaged across trials. The mean of the 3 largest mCSAs (cm\(^2\)) was used as the measure of muscle size.

**Specific Strength and Specific Power.** Peak isometric torque and power were normalized to mCSA, to estimate specific strength (Nm cm\(^{-2}\)) and specific power (W cm\(^{-2}\)), respectively.
Statistical Analyses

All statistical analyses were performed using Statistical Analysis Software (SAS Institute Inc., version 8.0, Cary, NC). Normality tests were conducted on all variables to determine the appropriate statistical tests for group comparisons.

The following tests were performed to address our hypotheses. Analysis of variance (ANOVA) was used to detect group differences in peak isometric torque, peak power, mCSA, specific strength, specific power, RFD, maxMUDR, and voluntary RFD in the KE muscle group. Age, gender and physical activity were used as covariates in all ANOVA tests, because of their known effects on muscle function. Non-normally distributed variables (peak isometric torque, maxMUDR, voluntary RFD, stimulated RFD) were log-transformed and verified for normality prior to performing the ANOVA. To detect differences in spasticity (KF passive torque) and its effect on KE power across the range of velocities (percentage of KF passive-to-KE voluntary torque), a 2-factor (group, velocity) repeated measures ANOVA was used. If significant interactions (p ≤ 0.05) were observed, Tukey’s post-hoc test was used to determine where group differences occurred.

Statistical analyses were also performed on the descriptive and secondary outcome variables. Unpaired t-tests were used to detect group differences in age, height, mass, BMI, foot-tap speed, and MFIS score. Wilcoxon tests were used to detect group differences in physical activity, chair rise time, 7.62 m walk time (usual and brisk pace), FSS and VAFS. Analysis of variance (ANOVA) with covariates of age, gender and physical activity level was used to detect group differences in velocity at which peak power was achieved, KF MVIC, peak power, coefficient of variation of mean
motor unit firings, and stimulated torque. Because the velocity at which peak power was achieved was not normally distributed, this measure was log-transformed prior to performing the ANOVA. Two-factor (group, velocity) repeated measures ANOVA was used to detect group differences in power and specific power across the range of velocities. If significant interactions (p ≤ 0.05) were observed, Tukey’s post-hoc test was used to determine where group differences occurred.

Linear regressions were performed to examine associations of strength and power with mechanisms of weakness and physical function. These regressions were used to clarify the contributions of each mechanism of force production to muscle weakness in MS, as well as the impact of weakness on physical function. An interaction term was included in the regression model to test if there were significant group differences in the associations of strength and power with mCSA and maxMUDR.

Means ± SD and precise p-values are presented throughout the document, including figures and tables. Significance level was set at p ≤ 0.05.

Results

Group Characteristics

Age, height, mass, BMI, and physical activity level were not different between groups (Table 5.1). Compared with non-MS controls, the MS group had greater symptomatic fatigue (MFIS, FSS, VAFS), longer time to complete 5 chair rises, lower foot-tap speed, and slower walk times (Table 5.1). One individual with MS was unable to perform the chair rise task without the use of her arms; she also had a 3- to 4-fold higher time to complete the 7.62 m walk at usual and brisk pace (19.5 s and 18.5 s,
respectively) relative to the MS group. Therefore, this individual’s values were not included in the statistical analyses for group differences in chair rise and walk times.

**Muscle Weakness in MS**

Individuals with MS had lower MVIC torque in the KE (Table 5.2) and KF (46 ± 13 Nm and 64 ± 22 Nm, p=0.0007, respectively) muscles, compared with controls. There was a group effect for KE power across velocities that showed lower power production in persons with MS compared with controls (p=0.02; Figure 5.2), with no group-by-velocity interaction (p=0.13). Peak power in the KE was lower in MS than control (Table 5.2). The velocity at which peak power was achieved was similar across groups (controls: 272 ± 36 °·s⁻¹, MS: 251 ± 45 °·s⁻¹, p=0.16). Peak torque and power were both positively associated with chair rise time, timed 7.62 m usual and brisk walk times, and FSS (Table 5.3; see Appendix C for figures).

**Neural Mechanisms**

*Motor Unit Discharge Rates.* When participants were asked to perform an MVIC with the needle inserted into the muscle for the MUDR recordings, the average relative torque achieved tended to be lower in control (81 ± 10 % of baseline MVIC) compared with MS (88 ± 9 % of baseline MVIC, p=0.06). A total of 179 motor units were identified (97 for control and 82 for MS). Maximal MUDR during the MVIC was lower in MS (22.7 ± 7.9 pps) compared with control (28.5 ± 8.1 pps, p=0.04; Figure 5.3). The coefficient of variation of mean motor unit firings were not different between groups (controls: 0.188 ± 0.054, MS: 0.172 ± 0.086, p=0.32). Maximal MUDR was associated with peak torque and peak power (Figure 5.4). Within the control group, maxMUDR was not associated with peak torque (r=0.45, p=0.11) and peak power
Within the MS group, maxMUDR was associated with peak power
(r=0.57, p=0.03) but not peak torque (r=0.35, p=0.23). There were no significant
differences in the associations (torque-by-maxMUDR interaction, p=0.61; power-by-
maxMUDR interaction, p=0.39) between groups.

**Spasticity.** Knee flexor passive torque across all velocities was not different
between groups (p=0.31; Figure 5.5A), and there was no significant group-by-velocity
interaction (p=0.22). Persons with MS tended to have a higher percentage of KF
passive-to-KE voluntary torque (Figure 5.5B), and there was no group-by-velocity
interaction (p=0.56).

Due to the large amount of variability in spasticity within the MS group,
individuals with MS were separated into 2 sub-groups: those with spasticity (passive
torque ≥ 2 SD above controls; n=5) and a non-spastic group (passive torque <2 SD from
mean for controls; n=9). Those individuals with spasticity had higher KF passive
torque compared with the non-spastic group (p=0.0001; Figure 5.6A), indicating
significant KF spasticity in these individuals. A significant group-by-velocity
interaction (p=0.0001) indicated that these individuals had greater passive torque at
velocities from 180 °·s⁻¹ to 300 °·s⁻¹. Further, the percentage of KF passive-to-KE
voluntary torque was higher in this subset compared to the non-spastic MS sub-group
(p<0.0001; Figure 5.6B). A significant group-by-velocity interaction (p<0.0001)
showed that those with spasticity had a greater percentage of KF passive-to-KE
voluntary torque at velocities of 210 °·s⁻¹ to 300 °·s⁻¹. There were no differences in
isometric torque, power, or any measures of force production between individuals with
and without spasticity in MS (p≥ 0.11; Appendix D). Notably, within the MS group,
spasticity was modestly associated with physical activity and walk times ($r \geq 0.51$, $p \leq 0.08$), but not associated with time to complete chair rises ($r=0.10$, $p=0.70$; Appendix E).

*Voluntary Rate of Force Development.* Neither the maximal voluntary RFD, nor the voluntary RFD normalized to stimulated RFD, were different between groups (Table 5.2). These results suggest no slowing of neural activation of the muscle during an isometric contraction in the MS group compared with controls.

**Muscle Mechanisms**

*Muscle Size.* Knee extensor mCSA was lower in MS ($n=14$) compared with control ($n=11$; Table 5.2). Muscle size was associated with peak isometric torque and peak power (Figure 5.7), for all participants combined. Within each group, muscle size was associated with peak isometric torque (control: $r=0.77$, $p=0.006$; MS: $r=0.63$, $p=0.02$) and peak power (control: $r=0.72$, $p=0.013$; MS: $r=0.61$, $p=0.022$). There were no significant differences in the associations (torque*mCSA, $p=0.79$; power*mCSA, $p=0.995$) between groups.

*Specific Strength and Specific Power.* There were no group differences in specific strength, but specific power was lower in MS compared with control (Table 5.2). Specific power across velocities was lower in MS ($n=14$) than control ($n=11$; $p=0.05$; Figure 5.8), with no group-by-velocity interaction ($p=0.38$). Maximal MUDR tended to be associated with specific power ($r=0.55$, $p=0.06$) for all participants combined. There was no association within each group between maxMUDR and specific power (control: $r=0.72$, $p=0.11$; MS: $r=0.45$, $p=0.79$).
Contractile Function. The rate of force development in response to a stimulated contraction was not different between MS and control (Table 5.2), suggesting that rate of cross-bridge cycling is similar across groups.

Discussion

The aim of this study was to identify the mechanisms of muscle weakness in persons with MS. As we hypothesized, persons with MS had lower isometric strength, power, MUDR, specific power, and smaller muscle size compared with controls. Contrary to our hypotheses, we showed no difference in specific strength, measures of spasticity, voluntary RFD, and stimulated RFD between persons with MS and controls. Therefore, the primary mechanisms of weakness in MS were lower MUDR and smaller muscle size. Differences in peak isometric torques were abolished when torque was normalized to muscle size, indicating that smaller muscle size explains a large portion of lower isometric strength. However, differences in peak dynamic power were reduced when power was normalized to muscle size, but specific power remained lower in persons with MS compared with controls. These data suggest that neural factors (i.e., MUDR), in addition to smaller muscle size, explain a portion of lower dynamic power in persons with MS. Thus, the mechanisms of weakness in MS may be specific to the contraction mode.

Muscle weakness in MS

We observed that moderately-impaired persons with MS had lower KE strength (23%), KF strength (29%) and KE power (32%) compared with controls. Our results agree with previous studies that have shown 16-57% deficits in isometric (18; 80; 82;
83; 111; 113) and dynamic (3; 16; 21; 63; 99; 121) torque in persons with MS compared with controls. Isometric strength and peak power, respectively, appeared to explain on average ~22% and ~17% of the variance in physical function. These associations suggest that muscle weakness may partially affect the performance of activities of daily living. In addition, we observed that isometric strength and power were associated with FSS, but not MFIS or VAFS. The FSS consists of 9-items that focus on physical fatigue, whereas the 21-item MFIS focus on physical and mental fatigue and the VAFS describes global fatigue. Thus, muscle weakness may partially explain physical fatigue experienced by some of the participants.

**Smaller muscles, similar specific strength, and lower specific power in MS**

The KE have been shown to be vulnerable to atrophy during disuse in the elderly (1; 27). Despite no group difference in physical activity (Table 5.1), we showed that persons with MS had a 17% lower maximal mCSA compared with controls. In this study, the mCSA values were comparable to those observed by White et al. (127) in the KE. Muscle size accounted for ~55% of the variance in isometric strength and dynamic power (Figure 5.7), indicating that smaller muscle size explains a significant portion of the muscle weakness observed in persons with MS. This relationship has also been observed in the elderly in the ankle dorsiflexor muscles (56).

Specific strength of the KE was not different between MS and control, suggesting that muscle quality was similar across groups in the isometric condition. This result agrees with Kent-Braun et al. (57), who observed no difference between MS and control in specific strength of the ankle dorsiflexors. To our knowledge, we are the first to show lower specific power in MS compared with control, suggesting that neural
factors, such as lower MUDR, were likely explaining lower peak power production in MS.

**No difference in the RFD during a stimulated contraction across groups**

The maximum RFD elicited by electrical stimulation has been used in previous studies as a measure of the rate of cross-bridge cycling (28; 30; 113). We observed no difference in the RFD in the KE between persons with and without MS, suggesting that the rate of cross-bridge cycling was similar across groups. De Haan et al. (28) have observed no differences in RFD between MS and control, using a current intensity to elicit 30% MVIC in the KE. The lack of difference in RFD between groups may be that the current intensity used to elicit submaximal torque was insufficient to recruit all muscle fibers. However, using a supramaximal stimulus, de Ruiter et al. (30) showed similar RFD across groups in the adductor pollicis muscle, whereas Sharma et al. (113) showed lower RFD in the ankle dorsiflexors in MS compared with control. At the single fiber level, cross-bridge kinetics were not different between persons with MS and controls (17; 44), supporting our observations. Thus, cross-bridge kinetics are likely not a mechanism for muscle weakness in persons with MS.

**Slower MUDR in persons with MS**

We observed that persons with MS had ~20% slower maximal MUDR in the vastus lateralis muscle compared with controls. Only one other study has examined MUDR during a MVIC and observed ~ 46% lower maxMUDR in a small group of 4 ambulatory persons with MS compared with 16 controls (106). Notably, motor unit discharge variability during a maximal voluntary contraction was not different between groups, suggesting that the pattern of motor unit discharges is similar between MS and
control. No studies have examined motor unit discharge variability during maximal contractions in persons with MS compared with control. However, Dorfman et al. (33) observed increased motor unit discharge variability in MS compared with control during submaximal contractions in various muscle groups (brachial biceps, brachial triceps, anterior tibial).

Slower rate-coding may be a consequence of demyelination in MS, generating prolonged motor conduction (12; 43; 123) and after-hyperpolarization period (10; 12) in persons with MS. Redistribution of sodium channels in the demyelinated areas of the axon (25) may explain the slowed recovery of the motor neuron (10; 12). Maximal MUDR may account for ~31% and 26% of the variance in isometric strength and power, respectively, indicating the importance of rate-coding on both contraction modes. In addition, maximal MUDR was shown to explain 25% of the variance in specific power, suggesting that rate-coding may be one mechanism of specific power.

**Spasticity in MS**

Spasticity can be a significant problem in persons with MS. Spasticity in an antagonist muscle is a potential mechanism for power loss in an agonist muscle, because of the antagonist’s resistance to passive movement due to a hyperexcitable stretch reflex (64). Antagonist co-activation may slow the velocity of a dynamic contraction and, thus, decrease the power generated by an agonist muscle. This phenomenon could explain some of the muscle weakness in MS, particularly during high-velocity contractions. Using the dynamometer, we showed no difference in KF passive torque during knee extension between persons with MS and controls. The percentage of KF passive-to-KE voluntary torque was slightly higher in persons with
MS compared with controls, although this was not statistically significant. In a sub-
group of individuals with spasticity, we observed higher contributions of KF passive
torque to lower KE voluntary torque compared with a non-spastic group during
maximal voluntary dynamic contractions (Figure 5.6). However, a larger sample of
individuals with and without spasticity in MS is needed to elucidate the role of
spasticity on physical activity and physical function.

Contrary to our findings, Nuyens et al. (90) observed a velocity-dependent
increase in KE and KF passive torque production at the muscle’s most stretched
position in persons with MS. The discrepancy between studies may be due to different
populations of MS individuals studied. We recruited mild-to-moderately impaired,
ambulatory individuals with MS; whereas Nuyens et al. (90) studied highly-impaired
persons with MS, most of whom used wheelchairs. Spasticity may reside in muscles
other than the knee flexors, and future studies are needed to clarify the contribution of
antagonist muscle spasticity on agonist power production in other muscle groups.

The measure of spasticity using the dynamometer is not without limitations.
Although settings were made to dictate the velocity of passive movement, target
velocity was not achieved during passive movements at settings >180 °·s⁻¹, due to
constraints in the dynamometer preset by the manufacturer. Because we were interested
in examining the effect of KF spasticity on KE power production, a quadratic equation
was determined for each individual to estimate torque resistance at the same velocities
achieved by each person during maximal voluntary dynamic contractions, to overcome
the limitations of the dynamometer. A major assumption in this approach was that
resistive torque at velocities greater than >180 °·s⁻¹ would increase in a quadratic
manner. Overcoming this limitation in the acceleration setting would allow a better understanding of the passive torque-velocity relationship to characterize spasticity.

**Voluntary RFD is not different across groups**

We observed no difference in either voluntary RFD or normalized RFD between MS and control (Table 5.2), suggesting that neural activation of force production was not different across groups during an isometric contraction. This data supports our lack of difference in specific strength, where group differences in isometric strength were abolished when torque was normalized to muscle size. High frequency bursts of motor unit discharges have been observed in young men during voluntary rate of force development during fast, ballistic contractions (32). Thus, during isometric contractions, muscle activation pattern may not be different between persons with MS and controls.

Although Desmedt et al. (32) showed high rate-coding during ballistic isometric contractions, the results provide some insight to the potential role of rate-coding in contraction velocity of power production. Because dynamic contractions were ballistic, rate-coding may have had a substantial role in producing maximal power, particularly during high-velocity contractions. It may be that rate-coding during force development may not be different between MS and control and likely explain the lack of difference in RFD across groups. Unfortunately, we were not able to reliably measure rate-coding during dynamic contractions, due to noise artifacts and the loss of motor unit potentials, particularly during rapid movement.
Future Directions

In this study, we have shown differences in isometric strength, power, specific power, MUDR and muscle size between persons with and without MS. Previous research has shown that resistance training can improve all of these variables. Resistance training has been shown to be effective in increasing strength and power in persons with MS (31; 48; 118; 127). However, the specific adaptations explaining the increase in isometric strength and power have not been determined. It is well recognized that long-term resistance training can increase muscle size. Neural adaptations have also been shown to occur during short-term resistance training in non-MS adults (52; 69; 95; 122). Studies in older adults have shown increases in maximal motor unit discharge rates (52) and a reduction in antagonist co-activation (49) following resistance training. Because the pathophysiology of MS affects the central nervous system, it is not known whether neural adaptations would be blunted following short-term resistance training. However, resistance training studies in MS showed improvements in power without increases in muscle mass (115; 127), suggesting that neural factors may be contributing to improvements in power production. Additional studies are needed to determine the mechanistic adaptations to a resistance training program in persons with MS.

Conclusion

The important mechanisms of muscle weakness in MS appear to be smaller muscle size and lower MUDR, each of which may contribute differently to weakness depending on contraction mode. The identification of these mechanisms provides an evidence-based rationale for the use of a resistance training intervention to increase
strength and power in persons with MS. The improvement and maintenance of neural activation and muscle size through resistance training may allow persons with MS to increase their physical activity, manage symptoms of MS, and improve their quality of life.
Acknowledgements

The authors thank the volunteers for participating in this study. We thank the Central New England Chapter of the National Multiple Sclerosis Society (NMSS) for its assistance in recruitment. We thank Anita Christie, Ph.D., Graham Caldwell, Ph.D., Erin Snook, Ph.D., and Stephanie Jones, M.S. for their helpful suggestions with different aspects of data collection and analyses.
Figure legends

5.1. Spasticity data for a female with MS. A) Individual torque traces during knee extension for each velocity, corrected for torque due to inertia. The x-axis represents the range of motion with 0° being the starting position of 90° flexion. B) Net torque traces, calculated by subtracting torque from 10 °·s⁻¹ for each velocity to correct for gravity and visco-elastic properties of the muscle. Torque was averaged across 20-50° extension, indicated by the bar. C) Torque averaged across 20-50° extension, for each velocity. The data were fit to a second-order polynomial and the derived equation was used to estimate torque at the same velocities achieved during voluntary dynamic contractions.

5.2. MS had lower KE power across velocities compared with control (p=0.02). Data are mean ± S.D. n=14 in each group.

5.3. Lower maximal MUDR of the vastus lateralis muscle was observed in persons with MS (22.7 ± 7.9 pps) compared with controls (28.5 ± 8.1 pps, p=0.04) during maximal voluntary isometric contractions. n=14 in each group. Square symbols denote group mean with standard deviation bars. Circles and triangles represent women and men, respectively.

5.4. Maximal MUDR was associated with peak isometric torque (A; r=0.56, p=0.002) and peak dynamic power (B; r=0.51, p=0.005). n=14 in each group for each variable. Within the control group, maxMUDR was not associated with peak torque (r=0.45, p=0.11) and peak power (r=0.48, p=0.09). Within the MS group, max MUDR was associated with peak power (r=0.57, p=0.03) but not peak torque (r=0.35, p=0.23).
5.5. There was no difference in KF passive torque (A) between MS and control (p=0.31). MS tended to have a higher percentage of KF passive-to-KE voluntary torque (B) compared with controls (p=0.067). Data are mean ± S.D. n=14 in each group.

5.6. Participants with MS were separated into 2 sub-groups: those with spasticity (passive torque ≥2 SD above control; n=5) and a non-spastic group (passive torque <2 SD from mean for controls; n=9). Individuals with spasticity had higher KF passive torque compared with the non-spastic sub-group (p=0.0001; A). Further, the percentage of KF passive-to-KE voluntary torque was higher in persons with spasticity than non-spastic sub-group (p<0.0001; B). * indicates a significant group x velocity interaction (p<0.0001).

5.7. Knee extensor muscle size is associated with peak isometric torque (A; r=0.75, p<0.001) and peak power (B; r=0.74, p<0.0001). Within each group, muscle size was associated with peak isometric torque (control: r=0.77, p=0.006; MS: r=0.63, p=0.02) and peak power (control: r=0.72, p=0.013; MS: r=0.61, p=0.022). n=14 in each group for isometric torque and power. For mCSA, n=11 for control and n=14 for MS.

5.8. MS (n=14) had lower specific power across velocities compared with control (n=11; p=0.05). Data are mean ± S.D.
Table 5.1. Group Characteristics

Data are presented as means ± S.D. C.I., 95% confidence interval for the difference in means across groups; BMI, body mass index; MFIS, Modified Fatigue Impact Scale; FSS, Fatigue Severity Scale; VAFS, Visual Analog Fatigue Scale. --, no C.I. because variables were non-normally distributed. All variables have n=14 in each group, except for chair rise and 7.62 m walk times (n=14 controls, 13 MS).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>MS</th>
<th>C.I.</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46 ± 7</td>
<td>48 ± 9</td>
<td>-8.5, 4.2</td>
<td>0.49</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.68 ± 0.10</td>
<td>1.66 ± 0.08</td>
<td>-0.05, 0.09</td>
<td>0.53</td>
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<tr>
<td>Mass (kg)</td>
<td>73.4 ± 16.3</td>
<td>74.7 ± 13.6</td>
<td>-13.0, 10.4</td>
<td>0.82</td>
</tr>
<tr>
<td>BMI (kg·m⁻²)</td>
<td>25.7 ± 4.4</td>
<td>26.9 ± 4.1</td>
<td>-4.5, 2.0</td>
<td>0.44</td>
</tr>
<tr>
<td>Physical Activity (counts·day⁻¹·1000⁻¹)</td>
<td>259 ± 146</td>
<td>193 ± 92</td>
<td>--</td>
<td>0.26</td>
</tr>
<tr>
<td>MFIS</td>
<td>15 ± 15</td>
<td>37 ± 14</td>
<td>-32.7, -10.0</td>
<td>0.0006</td>
</tr>
<tr>
<td>FSS</td>
<td>2.3 ± 1.1</td>
<td>4.5 ± 1.8</td>
<td>--</td>
<td>0.002</td>
</tr>
<tr>
<td>VAFS</td>
<td>1.5 ± 0.7</td>
<td>2.7 ± 1.9</td>
<td>--</td>
<td>0.02</td>
</tr>
<tr>
<td>Chair rise time (s)</td>
<td>8.26 ± 2.09</td>
<td>12.93 ± 4.13</td>
<td>--</td>
<td>0.001</td>
</tr>
<tr>
<td>Foot-tap speed (counts in 10 s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>left</td>
<td>47 ± 10</td>
<td>35 ± 7</td>
<td>5.3, 18.7</td>
<td>0.001</td>
</tr>
<tr>
<td>right</td>
<td>50 ± 10</td>
<td>36 ± 8</td>
<td>7.1, 21.5</td>
<td>0.004</td>
</tr>
<tr>
<td>7.62 m walk time (s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>usual</td>
<td>5.08 ± 0.60</td>
<td>6.02 ± 0.91</td>
<td>--</td>
<td>0.01</td>
</tr>
<tr>
<td>brisk</td>
<td>3.86 ± 0.45</td>
<td>4.47 ± 0.83</td>
<td>--</td>
<td>0.06</td>
</tr>
</tbody>
</table>
**Table 5.2. Knee Extensor Muscle Characteristics**

Data are presented as means ± S.D. mCSA, fat-free muscle cross-sectional area; RFD, maximal rate of force development. Voluntary RFD was normalized to stimulated RFD and expressed as a percentage. All variables have n=14 in each group, except mCSA, peak specific strength and peak specific power (n=11 controls, 14 MS).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>MS</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak Isometric Torque (Nm)</td>
<td>140 ± 51</td>
<td>108 ± 29</td>
<td>0.03</td>
</tr>
<tr>
<td>Peak Power (W)</td>
<td>320 ± 136</td>
<td>216 ± 73</td>
<td>0.002</td>
</tr>
<tr>
<td>mCSA (cm²)</td>
<td>52.9 ± 14.8</td>
<td>43.9 ± 7.8</td>
<td>0.04</td>
</tr>
<tr>
<td>Specific Strength (Nm·cm⁻²)</td>
<td>2.63 ± 0.67</td>
<td>2.46 ± 0.49</td>
<td>0.48</td>
</tr>
<tr>
<td>Specific Power (W·cm⁻²)</td>
<td>6.09 ± 1.69</td>
<td>4.92 ± 1.28</td>
<td>0.05</td>
</tr>
<tr>
<td>Stimulated RFD (% peak force·ms⁻¹)</td>
<td>1.24 ± 0.29</td>
<td>1.15 ± 0.39</td>
<td>0.37</td>
</tr>
<tr>
<td>Voluntary RFD (% peak force·ms⁻¹)</td>
<td>0.66 ± 0.29</td>
<td>0.64 ± 0.20</td>
<td>0.81</td>
</tr>
<tr>
<td>Voluntary-to-simulated RFD*100 (%)</td>
<td>53 ± 17</td>
<td>58 ± 21</td>
<td>0.44</td>
</tr>
</tbody>
</table>
Table 5.3. Associations between KE strength, peak power, physical function and symptomatic fatigue

FSS, Fatigue Severity Scale; MFIS, Modified Fatigue Impact Scale; VAFS, Visual Analog Fatigue Scale.

<table>
<thead>
<tr>
<th>Variable</th>
<th>KE strength (Nm)</th>
<th>KE peak power (W)</th>
<th>r</th>
<th>p-value</th>
<th>r</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chair rise time (s)</td>
<td>0.42</td>
<td>0.03</td>
<td>0.44</td>
<td>0.02</td>
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<tr>
<td>7.62 m walk time (s)</td>
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<tr>
<td>usual</td>
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<td>0.02</td>
<td>0.39</td>
<td>0.04</td>
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<td></td>
</tr>
<tr>
<td>brisk</td>
<td>0.53</td>
<td>0.005</td>
<td>0.42</td>
<td>0.03</td>
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<td></td>
</tr>
<tr>
<td>FSS</td>
<td>1.00</td>
<td>&lt;0.0001</td>
<td>0.44</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MFIS</td>
<td>0.32</td>
<td>0.10</td>
<td>0.28</td>
<td>0.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAFS</td>
<td>0.26</td>
<td>0.19</td>
<td>0.17</td>
<td>0.40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 5.1. Spasticity data for a female with MS

A) Individual torque traces during knee extension for each velocity, corrected for torque due to inertia. The x-axis represents the range of motion with 0° being the starting position of 90° flexion.

B) Net torque traces, calculated by subtracting torque from 10°·s\(^{-1}\) for each velocity to correct for gravity and visco-elastic properties of the muscle. Torque was averaged across 20-50° extension, indicated by the bar.

C) Torque averaged across 20-50° extension, for each velocity. The data were fit to a second-order polynomial and the derived equation was used to estimate torque at the same velocities achieved during voluntary dynamic contractions for each participant.
Figure 5.2.

MS had lower KE power across velocities compared with control (p=0.02). Data are mean ± S.D. n=14 in each group.
Figure 5.3.

Lower maximal MUDR of the vastus lateralis muscle was observed in persons with MS (22.7 ± 7.9 pps) compared with controls (28.5 ± 8.1 pps, p=0.04) during maximal voluntary isometric contractions. n=14 in each group. Square symbols denote group mean with standard deviation bars. Circles and triangles represent women and men, respectively.
Maximal MUDR was associated with peak isometric torque (A; r=0.56, p=0.002) and peak dynamic power (B; r=0.51, p=0.005). Within the control group, maxMUDR was not associated with peak torque (r=0.45, p=0.11) and peak power (r=0.48, p=0.09). Within the MS group, max MUDR was associated with peak power (r=0.57, p=0.03) but not peak torque (r=0.35, p=0.23). n=14 in each group for each variable.
Figure 5.5.

There was no difference in KF passive torque (A) between MS and control (p=0.31). MS tended to have a higher percentage of KF passive-to-KE voluntary torque (B) compared with controls (p=0.067). Data are mean ± S.D. n=14 in each group.
Figure 5.6.

Participants with MS were separated into 2 sub-groups: those with spasticity (passive torque $\geq$ 2 SD above control; $n=5$) and a non-spastic group (passive torque < 2 SD from mean for controls; $n=9$). Individuals with spasticity had higher KF passive torque compared with the non-spastic sub-group ($p=0.0001$; A). Further, the percentage of KF passive-to-KE voluntary torque was higher in persons with spasticity than non-spastic sub-group ($p<0.0001$; B). * indicates a significant group x velocity interaction ($p<0.0001$).
Figure 5.7.

Knee extensor muscle size is associated with peak isometric torque (A; r=0.75, p<0.001) and peak power (B; r=0.74, p<0.0001). Within each group, muscle size was associated with peak isometric torque (control: r=0.77, p=0.006; MS: r=0.63, p=0.02) and peak power (control: r=0.72, p=0.013; MS: r=0.61, p=0.022). n=14 in each group for isometric torque and power. For mCSA, n=11 for control and n=14 for MS.
Figure 5.8.

MS (n=14) had lower specific power across velocities compared with control (n=11; p=0.05). Data are mean ± S.D.
CHAPTER 6
PRÉCIS OF DISSERTATION

Novelty

This dissertation study was the first to systematically address neural and muscular mechanisms of muscle weakness in persons with MS compared with age-matched controls. The results of this dissertation suggest that lower motor unit discharge rates and smaller muscle size are primary mechanisms of knee extensor weakness in MS. Differences in isometric strength across groups were abolished when torque was normalized to muscle size. Differences in dynamic power were lessened when muscle size was accounted for, but specific power remained lower in persons with MS compared with controls, suggesting that neural factors explain some of the lower power production in persons with MS. These results suggest that mechanisms of weakness in MS may be contraction-mode specific.

This dissertation study was also the first to examine the role of spasticity in the KF on dynamic power production in the KE. Spasticity in an antagonist muscle may impede the velocity component of power production in an agonist muscle. In persons with MS, 5 individuals with spasticity in the knee flexor muscles had higher KF passive torque, and the percentage of KF passive-to-KE voluntary torque was large during high-velocity contractions compared with a non-spastic subgroup. These results suggest that spasticity in an antagonist muscle may act to co-activate during agonist power production, and thereby, contribute to some of the weakness in persons with MS.
**Significance and Impact**

The significance of this dissertation study is identification of key mechanisms (lower motor unit discharge rates and smaller muscle size) of muscle weakness within the same sample population with MS compared with age-matched controls. The contribution of lower motor unit discharge rates and smaller muscle size has been shown to be contraction-mode dependent. While lower isometric strength was largely explained by smaller muscle size, lower dynamic power was attributed to changes in neural function, in addition to smaller muscle size. Muscle size and motor unit discharge rates have been shown to improve with a resistance training program in non-MS adults. Thus, this dissertation provides evidence-based knowledge for resistance training intervention to ameliorate weakness by specifically addressing muscle size and motor unit discharge rates in MS.

**Future Directions**

Study 1 of this dissertation has provided key mechanisms of weakness in person with MS: muscle atrophy and altered neural function. These results provide the foundation for the proposed Study 2 of this dissertation, examining the effect of 2 weeks of high-intensity resistance training (3 times per week) on muscle strength, power, motor unit discharge rates, and antagonist muscle co-activation in persons with and without MS. In general, short-term resistance training is known to improve neural factors of force production (69), such as increasing motor unit discharge rates (52) and reducing antagonist co-activation (49). Eight- to 10-week resistance training programs in persons with MS have demonstrated increases in strength and power (31; 115; 118; 127) without any increases in muscle size (115; 127), suggesting that neural adaptation
was largely accounting for strength and power improvements. However, no studies have specifically measured neural adaptation in persons with MS. Thus, Study 2 will elucidate whether neural adaptations (e.g., motor unit discharge rates) occur following short-term resistance training in persons with MS and whether the magnitude of neural adaptation is similar or blunted in persons with MS compared with controls.

Therapeutic interventions may need to target the weaker limb more so than both limbs together. Anecdotally, persons with MS have indicated that one limb presents more symptomatic problems than the other. Power asymmetry in the KE muscles has been observed in persons with MS (21). Because Study 1 examined only the weaker leg, it may be that therapeutic interventions will need to focus more on the weaker leg rather than both legs to minimize limb asymmetries, which have been associated with postural imbalances, lower physical function and symptomatic fatigue (21). Thus, it would be interesting to examine whether resistance training in the weaker limb minimizes power asymmetry and how the mechanisms of this improvement might affect the trained and untrained limbs in persons with MS.

Further research into the role of spasticity on power production in MS is needed. Spasticity has a tremendous impact on physical function and overall quality of life. Although we did not show spasticity in the KF in 9 of the 14 participants with MS, spasticity may reside in other muscle groups (e.g., knee extensors, plantarflexors) and may affect the opposing muscle’s ability to generate maximal power production. Quantifying spasticity in other muscles, and its impact on power production in opposing muscles, is warranted. In addition, the effects of resistance training on spasticity have not yet been explored in MS. A reduction of spasticity following an acute bout of
unloaded leg cycling has been observed in persons with MS (73; 74). Therefore, a combination of resistance training and cycling may be a more effective approach in mitigating symptoms of MS that affect force production.
APPENDIX A.

ENERGY COST OF WALKING, SYMPTOMATIC FATIGUE AND
PERCEIVED EXERTION IN PERSONS WITH MULTIPLE SCLEROSIS

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Key words: oxygen consumption, fatigue, exertion, mobility
Abstract

A higher energy cost of walking (Cw) is sometimes observed in persons with multiple sclerosis (MS), and could contribute to their greater symptomatic fatigue. **Objective:** To compare Cw at 3 walking speeds in MS and controls, and to examine the interactions between Cw, symptomatic fatigue and perceived exertion. **Design:** Non-randomized controlled study. **Setting:** Muscle Physiology and Energy Metabolism Laboratories. **Participants:** Ten persons with MS and 14 age-matched controls. **Main Outcome Measures:** Oxygen consumption (VO₂) was obtained by open-circuit spirometry and indirect calorimetry at rest and during treadmill walking at 0.6 m·s⁻¹ and 1.4 m·s⁻¹, and at a self-selected, preferred speed. Cw was calculated as net VO₂ (walking minus rest; ml·kg⁻¹·m⁻¹). Fatigue and perceived exertion were obtained using a visual analog fatigue scale and modified Borg scale, respectively. **Results:** Preferred speed was not different between groups. Cw was higher in MS compared with controls across all walking speeds (p=0.003), with a group-by-speed interaction indicating higher Cw in MS during 0.6 m·s⁻¹ (p=0.001), but not 1.4 m·s⁻¹ or preferred speeds, compared with controls. MS had greater fatigue and perceived exertion (p≤ 0.004) at all speeds compared with controls. Cw was associated with perceived exertion during slow and preferred speeds (r≥ 0.41, p≤ 0.05), but was not associated with fatigue (r≤ 0.35, p≥ 0.10). **Conclusions:** Despite similar preferred speeds, and Cw at preferred and fast speeds, this MS group exhibited higher fatigue and exertion at all walk speeds. However, only slow walking induced sufficient challenges to postural control to elicit higher energy costs in MS. These results suggest that increased postural demands on
individuals with MS at slower walking speeds may require increased muscular contributions to maintain balance.
Introduction

Multiple sclerosis (MS) is an auto-immune disease that is defined by demyelination of nerves in the central nervous system. Symptoms of MS include symptomatic fatigue, increased perceived exertion, balance problems, and difficulty in walking. These symptoms may have a major effect on the ability to perform activities of daily living and alter physical activity behaviors in persons with MS.

Gait abnormalities, such as slower gait speed (7; 21; 67; 70; 111; 120; 121), shorter stride length (7; 67; 121), lower cadence (7; 121), and prolonged double-support phase (7; 67) are often observed in persons with MS. Altered gait characteristics and a lower preferred walking speed may be functional strategies adopted by individuals with MS to minimize the risk of falling (21; 104), given that individuals with MS demonstrate compromised balance. However, these strategies may, in turn, increase the energy cost of walking (Cw), defined as the net rate of oxygen consumption (VO₂; walking minus resting) per body mass and distance traveled (ml O₂·kg⁻¹·m⁻¹).

The metabolic rate while walking primarily reflects the energy costs associated with muscle activation for maintenance of balance, coordination and posture while propelling the body forward. In healthy adults, the relationship between Cw and walking speed has been characterized as a U-shaped curve by Ralston (101); with the lowest VO₂ typically occurring at a preferred walking speed and higher VO₂ at lower and higher speeds, reflecting increased Cw. Individuals with MS have shown higher Cw, compared with controls, over a range of slow and fast treadmill walking speeds (91; 93), but not at preferred walking speed. This systematic alteration of Cw across a
range of speeds in individuals with MS may suggest their use of different postural control strategies compared with controls.

Fatigue, defined as an overwhelming sense of tiredness, is a highly problematic symptom of MS (61). It is reasonable to suppose that higher Cw may increase feelings of fatigue. This could occur both directly, as a result of higher energy expenditure, or indirectly as a result of elevated body core temperature (61; 126). Heat generated from higher amounts of muscular activity (i.e., reflecting higher Cw) may exacerbate symptomatic fatigue in persons with MS. In turn, a worsening of fatigue during walking, regardless of the cause, could contribute to higher levels of perceived exertion (or perceptual effort) in persons with MS compared with controls, an effect that could act to limit physical activity behavior in persons with MS.

Therefore, the aim of this study was to quantify the Cw associated with prescribed (slow and fast) and preferred walking speeds in persons with MS compared with age-matched controls, and to explore the relationships between Cw, fatigue, perceived exertion and physical activity in MS. We hypothesized that persons with MS would have higher Cw across all speeds compared with controls. We also hypothesized that symptomatic fatigue and ratings of perceived exertion (RPE) would be lower at preferred speed compared to the slow and fast speeds, due to lower Cw at this speed. Finally, we examined whether Cw was associated with symptomatic fatigue, perceived exertion or habitual physical activity level in our study groups.
Methods

Participants

Ten persons with MS (9 females, 1 male) and 14 age-matched individuals without MS (11 females, 3 males) gave signed informed consent, as approved by the Institutional Review Board at the University of Massachusetts, Amherst, and in compliance with the Declaration of Helsinki. Of the 10 individuals with MS, 9 had relapsing-remitting and 1 had primary progressive subtypes. Participants were recruited from the university and surrounding communities, as well as through the New England Chapter of the National MS Society.

Participants were excluded from the study if they had metabolic, non-MS neurological, cardiovascular or other major diseases; cognitive impairment or mental disorder that prevented them from following instructions; orthopedic injury or significant arthritis in the legs; or were unable to walk at a speed of 0.6 m·s⁻¹. Participants with MS were ambulatory: 7 walked unaided, and 3 needed a cane or Canadian crutch. No participant with MS had an exacerbation within 6 months prior to their involvement in the study. Disease duration was 12 ± 8 years (mean ± SD; range 4 to 27 years). Medications taken by the participants with MS included [# of participants]: immunomodulators [9], anti-depressants [4], anti-convulsants [3], anti-anxiety [3], anti-spasticity [2], medications for bladder control [2] and for wakefulness [2]. Five of the 14 controls were taking the following medications [# of participants]: birth control [2], levothyroxine [2] and prilosec [1].
**Study Design**

After an overnight fast (~9 hours), participants reported to the Muscle Physiology Laboratory between 7:00 and 10:00am, where they completed the informed consent process, self-reported Expanded Disability Status Scale (sEDSS (14)), medical history form, and Physical Activity Readiness Questionnaire (119). Height (m) and body mass (kg) were determined, and body mass index (BMI; kg·m⁻²) was calculated. Participants completed the Fatigue Severity Scale (FSS (60)) and Modified Fatigue Impact Scale (MFIS; 21-items from Fatigue Impact Scale (38)) to characterize participant’s fatigue status in the prior 2 and 4 weeks, respectively. Participants were asked to walk 7.62 m over ground at a brisk pace and then at a preferred pace. Each pace was performed twice, and the fastest time (s) for each pace was reported. Following these tests, measures of resting metabolic rate and \( C_w \) were collected in climate-controlled laboratories. Prior to leaving, participants were given an accelerometer (GT1M, Actigraph Inc., Pensacola, FL) to wear for 7 days to monitor habitual physical activity.

**Energy cost of walking**

Metabolic rate was measured at rest while the participant lay supine on a bed, and during the 3 treadmill walking speeds. Gas exchange measurements were obtained continuously throughout each test by open-circuit spirometry and indirect calorimetry (TrueMax2400 Metabolic Measurement System, Parvomedics, Salt Lake City, UT). Pneumotachometer (to measure volume) and standard gas (16.01% \( O_2 \) and 3.98% \( CO_2 \)) calibrations were performed prior to each testing session. As participants breathed using a one-way valve mouthpiece, expired air was collected and delivered to the
mixing chamber via a hose. A caliper was placed over the nose to ensure that breathing was through the mouth only. Participants were instructed to lay supine quietly on a bed for ~15 minutes to reach and maintain steady-state, defined as the balance between energy required by working muscles and the rate of ATP production (via oxidative metabolism). Then, metabolic measures were made for 6-8 min. Resting metabolic rate (VO$_{2\text{rest}}$) was recorded as the average rate during the final 2 minutes of this period.

Following measurement of VO$_{2\text{rest}}$, participants walked for ~5 min on a treadmill at each of the 3 speeds, in the following order: 0.6 m·s$^{-1}$, 1.4 m·s$^{-1}$, and at a self-selected, preferred speed. Walking speed was ordered in this way to 1) make certain that participants with MS were able to perform the slow walking speed (particularly with those who used walking aids), and 2) familiarize each person with the fast walking speed prior to determining their preferred walking speed. Preferred walking speed was determined in an oscillatory-decaying manner. Using ~10-s epochs, the investigator set fast and slow speeds, alternately, decreasing the range with each repetition until the participant indicated their usual walking speed. Verbal encouragement was provided to all participants during each walking speed. All participants with MS lightly touched the handrails for extra sensory support. A second investigator was positioned behind the treadmill to provide tactile feedback on the back if the participant was walking to close to the end of the treadmill. Seated rest periods of 5 to 10 min and cold drinks of water were provided between walking speeds.

For each speed trial, oxygen consumption (VO$_{2\text{walk};}$ ml·kg$^{-1}$·min$^{-1}$) was averaged over the final 2 minutes when steady-state was maintained, and the net VO$_2$ (walking
minus resting) was used to calculate \( C_w \) (ml O\(_2\)·kg\(^{-1}\)·m\(^{-1}\)) during slow (\( C_w_{\text{slow}} \)), fast (\( C_w_{\text{fast}} \)), and preferred (\( C_w_{\text{pref}} \)) walking speeds (Equation 1).

\[
C_w = \frac{V_{O_2\text{walk}} - V_{O_2\text{rest}}}{v}
\]

Equation 1

where \( v \) is treadmill speed (93).

**Symptomatic Fatigue and Rating of Perceived Exertion (RPE)**

Symptomatic fatigue and RPE were measured while standing quietly on the treadmill prior to the first walking trial and again immediately following each treadmill trial. Acute symptomatic fatigue was measured using the visual analog fatigue scale (VAFS) (112; 129). Participants were asked to draw a vertical line across a scale marked 1 through 10, with each number separated by 1 cm. A ruler was used to measure and score each VAFS, with a smaller score indicating less fatigue. The modified Borg scale was used to obtain RPE (13; 71; 129). For the post-walk measures, participants were asked to indicate the VAFS and RPE based on how they felt during the last 30 s of walking.

**Physical Activity**

Participants were given an accelerometer (Actigraph Inc., Pensacola, FL) to wear around the waist for 7 days during waking hours, to monitor habitual physical activity. An activity log was also provided for participants to record their daily activities. A minimum of 5 days were included in the analysis of physical activity. Days that were not typical of habitual physical activity, indicated by self-report on the activity log, were excluded. Data from the accelerometer were downloaded using Actigraph’s ActiLife software and exported to a Microsoft Excel spreadsheet. Total
daily accelerometer counts were averaged across days and divided by 1000 for ease of reporting (counts·day⁻¹·1000⁻¹) (81).

Statistical Analyses

All statistical analyses were performed using Statistical Analysis Software (SAS Institute Inc., version 8.0, Cary, NC). Normality tests were conducted on all variables prior to proceeding with the statistical analyses, to determine the appropriate use of parametric and non-parametric tests.

Unpaired t-tests were used to examine group differences in age, height, body mass, BMI, FSS, MFIS, 7.62 m walk time, preferred speed, and VO₂rest. Wilcoxon tests were used to examine group differences in physical activity and baseline VAFS. Two-factor (group, speed) repeated measures analysis of variance was used to detect differences between groups in Cw, RPE and VAFS across all walking speeds. Linear regression was used to examine associations between Cw and physical activity, as well as between Cw, fatigue and RPE at each walking speed. Data are presented as means ± SD, and precise p-values and 95% confidence intervals are reported where appropriate.

Results

Participants

Age, height, body mass, BMI, and physical activity were similar across groups (Table 1). Participants with MS scored 4.6 ± 1.1 (range 3 to 6, out of a possible 10) in the sEDSS. The MS group reported a significantly higher fatigue state (FSS) in the preceding 2 weeks compared with the control group, and a greater impact of fatigue on their lives (MFIS; Table 1). Participants with MS had slower 7.62 m walk times at both
brisk and preferred pace compared with controls (Table 1). Two individuals with MS (1 female, 1 male) were unable to perform the fast treadmill walking speed and were statistically treated as missing data points.

**Energy Cost of Walking**

The groups had similar VO$_{2\text{rest}}$ (MS: 2.82 ± 0.65 ml·kg$^{-1}$·min$^{-1}$, control: 2.71 ± 0.85 ml·kg$^{-1}$·min$^{-1}$, p=0.72) and preferred walking speed (MS: 0.97 ± 0.28 m·s$^{-1}$, control: 1.05 ± 0.17 m·s$^{-1}$, p=0.42). Overall, individuals with MS had higher Cw compared with controls across walking speeds (Figure 1; p=0.003). A significant group-by-velocity interaction (p=0.03) showed that persons with MS had significantly higher Cw compared with controls during the slow, but not fast or preferred, walking speed (p=0.001).

**Symptomatic Fatigue and RPE**

At baseline, the acute fatigue state was not different between groups (VAFS: 1.6 ± 1.0 in MS, 1.2 ± 0.4 in controls, p=0.72). Overall, fatigue (Figure 2; p=0.001) and RPE (Figure 3; p=0.004) were higher in persons with MS compared with controls for all walking speeds. There were no significant group-by-velocity interactions for fatigue (p=0.07) or RPE (p=0.11). Notably, RPE was significantly associated with Cw$_{\text{pref}}$ (r=0.57, p=0.006) and Cw$_{\text{slow}}$ (r=0.41, p=0.05) but not Cw$_{\text{fast}}$ (r=0.26, p=0.22; Figure 4). There were no associations between VAFS and Cw at any speed (r ≤ 0.35, p ≥ 0.10; Figure 5).

**Physical Activity**

Total daily physical activity counts were similar in MS and controls (Table 1). Physical activity was negatively associated with Cw$_{\text{slow}}$ (r=-0.44, p=0.03) and Cw$_{\text{fast}}$
(r=-0.55, p=0.008), but not Cw_{pref} (r=-0.14, p=0.49; Figure 6). Symptomatic fatigue was negatively associated with physical activity at all speeds (r \geq -0.49, p \leq 0.02). Ratings of perceived exertion were negatively associated with physical activity at slow (r=-0.52, p=0.01) and fast (r=-0.59, p=0.004), but not preferred (r=0.0, p=1.0), walking speeds.

**Discussion**

We examined the energy cost of walking in persons with MS compared with age-matched controls. In contrast to previous reports (93), we observed that Cw was higher at slow, but not preferred and fast, speed in persons with MS compared with controls. This result indicates that persons with MS may adopt different strategies while walking at slow versus faster speeds to maintain postural control. We also showed that symptomatic fatigue and perceived exertion were higher in persons with MS compared with controls, but only perceived exertion was associated with Cw. These results suggest that, in contrast to perceived exertion, symptomatic fatigue may not develop as a consequence of higher energy costs.

*Differential effects of speed on cost of walking in individuals with MS*

Resting metabolic rate (VO_{2rest}) was similar across groups, which has been shown previously (92; 93; 117). We showed that Cw was higher during slow, but not fast or preferred, walking in persons with MS compared with age-matched controls. The lack of group differences in Cw during preferred and fast walking indicates a similar strategy in maintaining posture between groups. Olgiati et al. (93) showed higher Cw in persons with MS compared with controls during treadmill walking at 2, 3,
4, and 5 km·h⁻¹ (0.6, 0.8, 1.1, and 1.4 m·s⁻¹, respectively), regardless of speed. In absolute terms, Cw in our MS group was lower than that reported by Olgiati et al. (93) (approximate range from slow to fast speeds: 0.33 to 0.22 ml·kg⁻¹·m⁻¹), which may be attributed to their sample population having greater mobility impairment (50% needed to use a walking aid) and, consequently, a greater need to activate more muscle to accomplish the task. Greater mobility impairment has been associated with higher Cw (72). Tantucci et al. (117) observed no difference in VO₂ during an incremental exercise test using the cycle ergometer between controls and mildly-impaired persons with MS (EDSS 0.75 ± 0.30 SD). The lack of difference in VO₂ may be explained by a lower postural challenge in persons with MS when using the cycle ergometer versus the treadmill.

In our MS group, Cw was highest at slow walking and lowest at preferred walking speeds (Figure 1). This pattern of Cw has been observed in spastic paresis (131) (MS, spinal cord injury, hemiparesis) and post-stroke (103) patients, suggesting that there may be greater muscular demand to maintain postural control during slow, rather than fast, walking in these neurological disease patients. Studies have shown that postural control in MS during quiet stance is compromised (21; 47). Altered functional strategies (minimal displacement of center of mass and smaller posterior shift in the center of pressure) have been observed during gait initiation in women with MS compared with controls (104), possibly to adjust for postural imbalances (21). To date, no studies have measured Cw and gait characteristics, concurrently, at different walking speeds in persons with MS compared with controls.
Although preferred treadmill speed was similar across groups, there was a large range of preferred treadmill speeds in both groups, which may be due to having to identify the preferred speed on the treadmill. Persons with MS (1.31 ± 0.21 m·s⁻¹) had lower usual 7.62 m walk speed over ground compared with controls (1.52 ± 0.19 m·s⁻¹). Notably, the preferred treadmill speed was lower than the usual 7.62 m walk speed (p<0.001) in both groups.

*Symptomatic Fatigue and Perceived Exertion are impacted differently during walking in individuals with MS*

Fatigue is a common, disabling symptom of MS (40). As expected, general fatigue state (FSS) and the impact of fatigue on quality of life (MFIS) were higher in individuals with MS compared with controls. Prior to the walking tests, acute fatigue (VAFS) did not differ between the MS and control groups. However, at the end of each walking trial, both fatigue and perceived exertion were higher in persons with MS compared with controls (Figures 2 and 3). However, acute fatigue was not associated with Cw, whereas perceived exertion was, suggesting that there may be other determinants (i.e., cognitive demands) affecting symptomatic fatigue than increased energy costs.

In contrast to our results, Morrison et al. (71) showed similar changes in perceived exertion and heart rate during a graded exercise test on a cycle ergometer between persons with MS and controls. The differences in perceived exertion observed between studies may be due to differences in the severity of MS and testing protocol. Morrison et al.’s MS group had a median EDSS score of 2.75 (71) compared with our median of 4.5 on the self-reported EDSS instrument. The difference in testing protocol
(whole-body walking versus cycling) may also have contributed to differences in outcome. Walking may demand more muscular activity to maintain upright posture than cycling in persons with MS compared with controls. In addition, we prescribed absolute speeds, whereas Morrison et al. (71) had participants perform at relative workloads (% peak VO₂), which may explain similar perceived exertion in persons with MS and controls. We observed that RPE was related to Cw, indicating that higher perceived exertion may be explained by higher Cw.

Unexpectedly (although there was no VAFS-by-speed or RPE-by-speed interaction), fatigue and RPE were lowest during slow walking, where Cw was at its highest; and highest during preferred and fast walking, where Cw was at its lowest. It is possible that fatigue and exertion worsened over time, given that the speeds were tested in order from slow to fast to preferred speeds. However, if this were the case, we would expect an incremental increase in fatigue and exertion following each walking bout. Instead we observed that fatigue and perceived exertion were not different between fast and preferred walking speeds. Because the preferred walking speed followed fast walking, it may be that the non-incremental increase in walking speed may have prevented any further exacerbation of fatigue and perceived exertion.

Altered Cost of Walking by individuals with MS is not related to Physical Activity

In this study, our groups had similar habitual physical activity based on total daily accelerometer counts. Using the same methodology, Ng and Kent-Braun (81) have shown lower physical activity in persons with MS (median EDSS score of 3.0) compared with controls. This discrepancy may be because we tried to control physical
activity level by recruiting individuals who were sedentary-to-recreationally active for both groups.

We observed that lower physical activity was related to higher Cw, suggesting that de-conditioning, rather than the symptoms of MS, may explain increased energy expenditure, given that we did not demonstrate group-specific differences in physical activity. Persons with lower physical activity may be weaker and have less muscular coordination, which may require more muscular activity to accomplish a given task. Benedetti et al. (6) observed a decline in Cw at 4 and 6 km·h⁻¹ (1.1 and 1.7 m·s⁻¹) following a 4-week treadmill walking intervention in 3 MS patients. In contrast, Olgiati et al. (92) observed no change in Cw in persons with MS, despite improvements in walking performance, following a 24-week physical therapy rehabilitation program. The discrepancy between these results may be the difference in the type of interventions (ramped treadmill walking exercise (6) versus general rehabilitation program (92)). Thus, increasing physical activity alone may not improve Cw in MS, but may depend on the type and intensity of the intervention.

Limitations

The walking protocol was conducted on a treadmill because walking over ground at prescribed speeds is difficult to control. In healthy adults, usual gait patterns that are normally observed while walking over ground may be altered (2) compared with walking on the treadmill at preferred speeds. Despite potential gait characteristic differences between treadmill and over ground walking, elevated Cw is likely attributed to postural control challenges in MS.
Another limitation to our walking protocol was that walking was conducted on the flat surface of a treadmill, whereas most walking environments are uneven. Thus, it is not possible in this study to determine whether Cw would be altered in MS compared with controls in a more ecological environment. However, the presence of sensory deficits in persons with MS could exacerbate this difference in Cw, as uneven surfaces could present an additional challenge to postural control during gait in these individuals.

Conclusion

Differences in Cw in persons with MS, compared with age-matched controls, are higher at slow speeds but appear to be abolished at faster speeds. Thus, slow walking may induce postural control challenges that require greater muscular work. Unlike perceived exertion, symptomatic fatigue appears to be dissociated from the energy costs of walking in MS. Symptomatic fatigue and perceived exertion may have an impact on habitual physical activity behavior, although this does not seem to be related specifically to the presence of MS.
Acknowledgements

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Table 1. Group Characteristics

Data are presented as means ± S.D. BMI, body mass index; CI, 95% confidence interval for the difference in means across groups. FSS, fatigue severity scale. MFIS, modified fatigue impact scale. 7.62 m walk time is for over ground walking. CI for physical activity is not provided due to the use of non-parametric analysis to test for group differences.

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LIST OF FIGURES

Figure 1. Energy cost of walking at 3 speeds. The cost of walking (Cw) was higher in persons with MS compared with controls, at all speeds (p=0.003). * indicates a significant group-by-speed interaction, where Cw at 0.6 m·s⁻¹ was higher in MS compared to controls (p=0.001). Data are presented as means ± S.D. Note that the order of trials was: slow, fast, preferred.

Figure 2. Acute symptomatic fatigue at 3 walking speeds. Visual analog fatigue scale (VAFS) score was higher in persons with MS than controls for all walking speeds (p=0.001). A VAFS score of 1 indicated “no fatigue” and 10 indicated “severe fatigue”. Data are presented as means ± S.D. Note that the order of trials was: slow, fast, preferred.

Figure 3. Ratings of perceived exertion at 3 walking speeds. Rating of perceived exertion (RPE) score was higher in persons with MS than controls for all walking speeds (p=0.004). A RPE score of 1 indicated “not tired at all” and 10 indicated “so tired I cannot go anymore”. Data are presented as means ± S.D. Note that the order of trials was: slow, fast, preferred.

Figure 4. Relationship between RPE and energy cost of walking. RPE was significantly associated with Cw pref and Cw slow, but not Cw fast. Closed circles=control. Open circles=MS.

Figure 5. Relationship between VAFS and energy cost of walking. There were no associations between VAFS and Cw at any speed. Closed circles=control. Open circles=MS.
Figure 6. Relationship between physical activity and energy cost of walking. Physical activity was associated with the cost of walking (C_w) at a) slow (C_{w,slow}) and c) fast (C_{w,fast}) speeds, but not at b) preferred speed (C_{w, pref}). Closed circles=control. Open circles=MS.
Figure 1. Energy cost of walking at 3 speeds
Figure 2. Acute symptomatic fatigue at 3 walking speeds
Figure 3. Ratings of perceived exertion at 3 walking speeds
Figure 4. Relationship between RPE and energy cost of walking

a) Cwslow (mL·kg⁻¹·m⁻¹)

b) Cwpref (mL·kg⁻¹·m⁻¹)

c) Cwfast (mL·kg⁻¹·m⁻¹)

r = 0.57, p = 0.006

r = 0.41, p = 0.05

r = 0.26, p = 0.22
Figure 5. Relationship between VAFS and energy cost of walking

a) $C_{w\text{slow}}$ (mL·kg$^{-1}$·m$^{-1}$)

b) $C_{w\text{pref}}$ (mL·kg$^{-1}$·m$^{-1}$)

c) $C_{w\text{fast}}$ (mL·kg$^{-1}$·m$^{-1}$)

r=0.35, p=0.10

r=0.30, p=0.15

r=0.20, p=0.35
Figure 6. Relationship between physical activity and energy cost of walking

a) $C_{w_{\text{slow}}}$ (mL·kg$^{-1}$·m$^{-1}$)

- $r = -0.44, p = 0.03$

b) $C_{w_{\text{fast}}}$ (mL·kg$^{-1}$·m$^{-1}$)

- $r = -0.14, p = 0.49$

c) $C_{w_{\text{pref}}}$ (mL·kg$^{-1}$·m$^{-1}$)

- $r = -0.55, p = 0.008$

Physical Activity (counts·day$^{-1}$·1000$^{-1}$)
# APPENDIX B

## LIST OF MEDICATIONS

<table>
<thead>
<tr>
<th>Medication</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albeuterol</td>
<td>bronchodilator</td>
</tr>
<tr>
<td>Amantadine</td>
<td>anti-viral agent</td>
</tr>
<tr>
<td>Amoxicilin</td>
<td>antibiotic</td>
</tr>
<tr>
<td>Aricept</td>
<td>reversible inhibitor of acetylcholinesterase</td>
</tr>
<tr>
<td>Aspirin</td>
<td>anti-inflammatory</td>
</tr>
<tr>
<td>Avonex</td>
<td>Immuno-modulator</td>
</tr>
<tr>
<td>Baclofen</td>
<td>muscle relaxant and anti-spastic agent</td>
</tr>
<tr>
<td>Botox</td>
<td>blocks nerve activity in muscle</td>
</tr>
<tr>
<td>Celexa</td>
<td>anti-depressant</td>
</tr>
<tr>
<td>Cellcept</td>
<td>immunosuppressive agent</td>
</tr>
<tr>
<td>Claritin</td>
<td>anti-histamine agent</td>
</tr>
<tr>
<td>Copaxone</td>
<td>reduce the frequency of relapses</td>
</tr>
<tr>
<td>Detrol-LA</td>
<td>treats symptoms of overactive bladder</td>
</tr>
<tr>
<td>DHEA</td>
<td>Precursor to sex hormones</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>anti-hypertensive agent; Ca+-channel blocker</td>
</tr>
<tr>
<td>Enablex</td>
<td>treats symptoms of overactive bladder</td>
</tr>
<tr>
<td>Flexeril</td>
<td>muscle relaxant</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>anti-depressant</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>anti-epileptic agent</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>anti-hypertensive agent; diuretic</td>
</tr>
<tr>
<td>Imitrex</td>
<td>treat migraines</td>
</tr>
<tr>
<td>IV steroid treatment</td>
<td>anti-inflammatory treatment to treat MS relapse</td>
</tr>
<tr>
<td>Klonopin</td>
<td>anti-epileptic agent</td>
</tr>
<tr>
<td>Lexapro</td>
<td>anti-depressant</td>
</tr>
<tr>
<td>Lipitor</td>
<td>cholesterol-lowering agent</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>anti-hypertensive agent; ACE inhibitor</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>anti-cancer agent</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>narcotic drug that blocks the effects of other narcotics</td>
</tr>
<tr>
<td>Neurontin</td>
<td>anti-epileptic agent</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>antibiotic</td>
</tr>
<tr>
<td>Oxytrol</td>
<td>treats symptoms of overactive bladder</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>anti-depressant</td>
</tr>
<tr>
<td>Prilosec</td>
<td>treats symptoms of gastroesophageal reflux disease</td>
</tr>
<tr>
<td>Provigil</td>
<td>promotes wakefulness</td>
</tr>
<tr>
<td>Re bif</td>
<td>immuno-modulator agent</td>
</tr>
<tr>
<td>Ritalin</td>
<td>mild CNS stimulant; improves attention</td>
</tr>
<tr>
<td>Rituxan IV infusion</td>
<td>Monoclonal antibody</td>
</tr>
<tr>
<td>Simvarstatin</td>
<td>cholesterol-lowering agent</td>
</tr>
<tr>
<td>Synthroid</td>
<td>treats hypothyroidism</td>
</tr>
</tbody>
</table>
Trazadone  anti-depressant
Unithroid  treats hypothyroidism
Vesicare  treats symptoms of overactive bladder
Vitamin D  vitamin D supplement
Wellbutrin  anti-depressant
Xanax  treats anxiety and panic disorder
Zoloft  anti-depressant
APPENDIX C

ASSOCIATIONS BETWEEN ISOMETRIC TORQUE, DYNAMIC POWER, AND PHYSICAL FUNCTION
### APPENDIX D

**COMPARISONS OF NEUROMUSCULAR VARIABLES BETWEEN NON-SPASTIC AND PERSONS WITH SPASTICITY**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-spastic</th>
<th>With spasticity</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak Isometric Torque (Nm)</td>
<td>107 ± 31</td>
<td>109 ± 30</td>
<td>0.91</td>
</tr>
<tr>
<td>Peak Power (W)</td>
<td>223 ± 71</td>
<td>204 ± 82</td>
<td>0.51</td>
</tr>
<tr>
<td>mCSA (cm²)</td>
<td>44.7 ± 9.1</td>
<td>42.3 ± 4.9</td>
<td>0.52</td>
</tr>
<tr>
<td>Specific Strength (Nm·cm⁻²)</td>
<td>2.41 ± 0.52</td>
<td>2.56 ± 0.46</td>
<td>0.58</td>
</tr>
<tr>
<td>Specific Power (W·cm⁻²)</td>
<td>4.98 ± 1.18</td>
<td>4.79 ± 1.57</td>
<td>0.82</td>
</tr>
<tr>
<td>maxMUDR (pps)</td>
<td>20.2 ± 5.8</td>
<td>27.2 ± 9.7</td>
<td>0.19</td>
</tr>
<tr>
<td>Stimulated RFD (% peak force·ms⁻¹)</td>
<td>1.10 ± 0.36</td>
<td>1.24 ± 0.46</td>
<td>0.58</td>
</tr>
<tr>
<td>Voluntary-to-simulated RFD*100 (%)</td>
<td>58.1 ± 20.0</td>
<td>58.9 ± 26.3</td>
<td>0.95</td>
</tr>
</tbody>
</table>

mCSA, fat-free muscle cross-sectional area; maxMUDR, maximal motor unit discharge rate; RFD, maximal rate of force development.
APPENDIX E

ASSOCIATIONS BETWEEN SPASTICITY AND PHYSICAL FUNCTION IN

PERSONS WITH MS

• = non-spastic  ○ = persons with spasticity

<table>
<thead>
<tr>
<th>Variable</th>
<th>MS Group</th>
<th>r</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical activity</td>
<td>All</td>
<td>-0.53</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Non-spastic</td>
<td>-0.04</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>Spastic</td>
<td>-0.87</td>
<td>0.06</td>
</tr>
<tr>
<td>Chair rise time</td>
<td>All</td>
<td>0.10</td>
<td>0.70</td>
</tr>
<tr>
<td></td>
<td>Non-spastic</td>
<td>0.70</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Spastic</td>
<td>-0.58</td>
<td>0.30</td>
</tr>
<tr>
<td>7.62 m usual walk time</td>
<td>All</td>
<td>0.52</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>Non-spastic</td>
<td>0.79</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Spastic</td>
<td>0.70</td>
<td>0.19</td>
</tr>
<tr>
<td>7.62 m brisk walk time</td>
<td>All</td>
<td>0.51</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>Non-spastic</td>
<td>0.79</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Spastic</td>
<td>0.40</td>
<td>0.51</td>
</tr>
</tbody>
</table>
APPENDIX F

ANCILLARY MEASURES TO CHAPTER 5

- To further characterize contractile function, the maximal rate of force relaxation (% peak force·ms⁻¹) was determined from the first derivative of the torque trace. The maximal rate of force relaxation was slower in persons with MS (-0.71 ± 0.22 % peak force·ms⁻¹) compared with controls (-1.05 ± 0.32 % peak force·ms⁻¹, p=0.0005). These results suggest slowing of calcium re-sequestration to the sarcoplasmic reticulum in persons with MS compared with controls.

- To examine maxMUDR at submaximal intensities, participants were asked to perform three 50% MVICs (4-5 s duration), with 2 min of rest between trials. Additional 50% MVIC trials were performed if there were less than 3 trials with clear recordings. A total of 138 motor units were identified (72 for controls and 66 for MS) at 50% MVIC. Three participants (2 controls, 1 MS) were unable to perform the intramuscular EMG protocol at 50% MVIC due to non-significant adverse event (e.g. feeling faint). Average torque achieved when asked to perform 50% MVIC was 50 ± 3 % for both controls and MS during MUDR recordings. Lower maxMUDR at 50% MVIC were observed in persons with MS (16.0 ± 4.6 pps) compared with controls (20.4 ± 5.9 pps, p=0.04). These results agree with Dorfman et al. (33), who observed lower maxMUDR at submaximal intensity contractions in persons with MS compared with controls.

- We also measured mean MUDR, which was calculated by averaging all interpulse intervals of a given motor unit during the plateau phase of each contraction, at 100% and 50% MVIC. There was no difference in mean MUDR at 100% MVIC across
groups (controls: 18.6 ± 5.1 pps, MS: 16.3 ± 5.7 pps, p=0.24). At 50% MVIC, lower mean MUDR were observed in persons with MS (10.8 ± 2.0 pps) compared with controls (13.8 ± 3.8 pps, p=0.02).

- We indirectly compared motor unit recruitment strategies by taking the ratio of MUDR between 100% and 50% MVIC for each participant. There were no differences across groups in the ratio of maximal (controls: 1.37 ± 1.38, and MS: 1.38 ± 0.23, p=0.87) and mean (controls: 1.33 ± 0.19, MS: 1.46 ± 0.32, p=0.23) MUDR at 100% and 50% MVIC.
APPENDIX G

TABLE OF UNIT CONVERSIONS

<table>
<thead>
<tr>
<th>m·s⁻¹</th>
<th>km·hr⁻¹</th>
<th>miles·hr⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.17</td>
<td>0.61</td>
<td>0.38</td>
</tr>
<tr>
<td>0.19</td>
<td>0.68</td>
<td>0.43</td>
</tr>
<tr>
<td>0.21</td>
<td>0.76</td>
<td>0.47</td>
</tr>
<tr>
<td>0.28</td>
<td>1.00</td>
<td>0.63</td>
</tr>
<tr>
<td>0.56</td>
<td>2.00</td>
<td>1.24</td>
</tr>
<tr>
<td>0.60</td>
<td>2.16</td>
<td>1.34</td>
</tr>
<tr>
<td>0.83</td>
<td>3.00</td>
<td>1.86</td>
</tr>
<tr>
<td>0.97</td>
<td>3.49</td>
<td>2.17</td>
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<tr>
<td>1.05</td>
<td>3.78</td>
<td>2.35</td>
</tr>
<tr>
<td>1.11</td>
<td>4.00</td>
<td>2.49</td>
</tr>
<tr>
<td>1.31</td>
<td>4.72</td>
<td>2.93</td>
</tr>
<tr>
<td>1.39</td>
<td>5.00</td>
<td>3.11</td>
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<td>1.52</td>
<td>5.47</td>
<td>3.40</td>
</tr>
<tr>
<td>1.67</td>
<td>6.00</td>
<td>3.73</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>m</th>
<th>ft</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.62</td>
<td>25</td>
</tr>
</tbody>
</table>
APPENDIX H

PARTICIPANT FORMS
Project Title: Mechanisms of Muscle Weakness in Persons with Multiple Sclerosis

Principal Investigator: Linda Chung, M.S.
Co-Investigators: Jane Kent-Braun, Ph.D., Richard van Emmerik, Ph.D.

Your written informed consent is required before you can participate in this project. Please read this document carefully and then sign your name on the last page if you agree to participate. This document is in accordance with the General Policy on the Rights and Welfare of Human Subjects, as approved by the Faculty Senate of the University of Massachusetts.

Purpose: To systematically determine the causes of reduced muscle strength and power, and how it impacts energy expenditure, physical function and symptomatic fatigue in persons with MS.

Eligibility: To participate in this study, you must
1) be between the ages of 30 and 60 years
2) be free from metabolic, non-MS neurologic, cardiovascular or other major disease
3) not be taking any medications (other than for MS) that may affect muscle function (i.e., beta blockers, sedatives, anti-cholesterol medications, etc.)
4) have a visual acuity of 20/200 or better
5) participate in less than three 30-minute structured exercise sessions per week
6) not be pregnant
7) not have cognitive impairment or a mental disorder that precludes following instructions
8) not have significant arthritis in the lower extremities
9) have no history of breathing difficulties, cramping, light-headedness or other symptoms of exertion
10) not be a smoker
11) not have oculomotor and/or cerebellar disorders
12) have no history of claustrophobia
13) not have pieces of metal in your body (such as fragment(s) in the eye, aneurysm clips, ear implants, spinal nerve stimulator, and pacemaker)

All persons with MS must also have clinically verified MS (any subtype).

Procedures: Prior to your participation in this study, you will be screened by telephone interview for general health status, medical history, current medications and usual physical activity habits. If you are qualified and agree to participate in the study, the following table outlines the measures we’ll be making in each visit. Each visit will be
separated by 3 to 7 days. A more detailed explanation of each of the measures are described below the table.

<table>
<thead>
<tr>
<th>Visit #</th>
<th>Measures</th>
<th>Location</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>• Questionnaires&lt;br&gt;• Anthropometrics&lt;br&gt;• Blood pressure&lt;br&gt;• Physical function&lt;br&gt;• Familiarization of dynamometer protocols&lt;br&gt;• Activity monitor instructions</td>
<td>Muscle Physiology Lab at UMass-Amherst</td>
<td>2.5 hours</td>
</tr>
<tr>
<td>2</td>
<td>• Dynamometer protocols on both legs&lt;br&gt;  • Passive resistance&lt;br&gt;  • Isometric contractions&lt;br&gt;  • Isovelocity contractions&lt;br&gt;  • Electrical stimulation</td>
<td>Muscle Physiology Lab at UMass-Amherst</td>
<td>2.5 hours</td>
</tr>
<tr>
<td>3</td>
<td>Intramuscular electromyography on both legs</td>
<td>Exercise Neuroscience Lab at UMass-Amherst</td>
<td>1.5 hours</td>
</tr>
<tr>
<td>4</td>
<td>MRI of both legs</td>
<td>MRI Center Cooley Dickinson Hospital in Amherst</td>
<td>1.5 hours</td>
</tr>
</tbody>
</table>

**Questionnaires.** You will be asked to complete the following questionnaires: medical history, self-reported expanded disability status score, modified fatigue impact scale, visual analog fatigue scale, spasticity scale, and physical activity readiness. You will also be asked to complete the magnetic resonance safety form to determine your eligibility to enter the MRI room.

**Anthropometrics.** We will measure your height, weight, and length of your lower limb.

**Blood pressure.** We will measure your blood pressure at the arm while you are lying down on a bed.

**Physical Function.** Your level of physical function will be measured using the following performance tests, which the investigator will demonstrate for you:

- **Metabolic Rate While Walking**
  - We will measure how much energy you expend while walking at 3 different speeds. To do this, we will first measure your resting metabolic rate (following an overnight fast). You will lay on a bed with a ventilated hood placed over your head for 20 minutes. The ventilated hood will measure the difference in oxygen between the air you breathe in and the air you breathe out during normal breathing.
  - Next, you will be asked to breathe through a mouthpiece, which will be connected to an indirect calorimeter via a hose, so that we can measure your metabolic rate while you are walking. You will be asked to walk on a treadmill at a self-selected speed.
pace, and at slow and fast speeds, for 4 minutes each. You will be given 5-10 minutes of seated rest between walking tests.

- **Walking speed**
  - You will be asked to walk 25 feet twice, once at a self-selected pace and once at a brisk pace.

- **Leg function**
  - To assess your leg strength, we will ask you to perform rapid chair rises 5 times

- **Foot tap speed**
  - You will be asked to perform rapid foot taps for 10 seconds for each foot.

**Familiarization to dynamometer protocols.** A dynamometer is an instrument that lets us measure the force your muscles produce while your leg is static, or moving at a fixed speed. You will be seated in a chair with your upper body secured with seat belt straps. Your lower leg will be secured to a rotating apparatus using Velcro. Using one of your legs, we will then familiarize you with the contraction protocols that you will perform (see Dynamometer Protocols below), so that you are comfortable with the procedures.

**Activity Monitor.** At the end of your Visit 1, you will be asked to wear an activity monitor around your waist for 7 days during waking hours. The activity monitor is a small plastic device (about the size of a pager) that measures vertical accelerations, and will give us an idea of your daily physical activity level. You will also be asked to keep a simple diary of your physical activities. You will return the activity monitor and diary on your next visit.

**Dynamometer protocols.** Prior to being seated on the dynamometer, you will be asked to warm-up your leg muscles by cycling on a recumbent bike for 2 minutes without any resistance. Following this warm-up, we will tape small electromyography electrodes to the skin on the front and back sides of your thigh, as well as on the bony part of your knee. Surface electromyography electrodes will measure the electrical activity from your muscles. Once you are seated and secured to the dynamometer (see Familiarization of Dynamometer Protocols), you will perform the following protocols:

- **Passive resistance.** While you are relaxed, the dynamometer will extend and flex your knee over a set range of motion at different speeds. The data obtained from this protocol will give us information about spasticity, which is defined as increased muscle tone or stiffness due to a hyper-excitile reflex.

- **Isometric contractions.** You will perform 3 to 4 static, maximal contractions of your quadriceps muscles (front of the thigh). Each contraction will last no longer than 5 seconds. You will repeat this with the hamstring muscles (back of the thigh).
- **Isovelocity contractions.** You will perform maximal voluntary contractions by extending your knee against different speeds of resistance. Your leg will move during muscle contraction, but the movement of your leg will be limited to a fixed range.

- **Electrical stimulation.** In addition to the surface electromyography electrodes, 2 flexible stimulating pads will be placed over your thigh. These pads are designed to stimulate your muscle to contract without any effort on your part, which will give us information about your muscle’s function. We will set the intensity of the stimulation to produce a force level that is 50% of your maximum voluntary strength. Once the intensity is set, we will give you a burst of stimuli that lasts 1 second while your leg remains in a static position and you stay relaxed. We will apply the same burst 2 more times, with 2 minutes of rest between each burst.

**Intramuscular Electromyography.** Like surface electromyography, electrical activity from your muscle will be measured using a small, sterilized needle electrode placed directly into your muscle. It will remain there for ~30-40 min. This will provide us precise information about your muscle activation. Electrical signals during submaximal and maximal voluntary isometric contractions will be recorded. To obtain clear electrical signals, slight adjustments of the electrode will be made. This procedure will be performed in the Exercise Neuroscience Lab, just down the hall from the Muscle Physiology Lab, and will be done in both legs.

**MRI.** An MRI of your thighs will be taken at the Cooley Dickinson Hospital MRI Center on University Drive in Amherst. We will provide transportation to Cooley Dickinson for you, if you wish. You will be asked to complete a brief medical history form and Magnetic Materials Safety questionnaire to ensure that there are no magnetic materials in your body. After we ensure that you are free of magnetic objects, you will be taken into the MRI room, where you will lie on the MRI bed and have your leg centered inside a circular coil. This coil, which is shaped like a small tube, will allow us to obtain information about the size and shape of your muscles, using radio waves and a superconducting magnet. To protect your hearing during the imaging, you will be given earplugs or headphones to wear. After you are positioned comfortably, we will slide the MRI bed into the scanner. We will then collect anatomical images of your leg. While acquiring images, the table may shake slightly, and you will hear loud knocking noises. This is a normal part of the imaging procedure. This procedure will take approximately 30 minutes per leg and both legs will be imaged.
**Possible Risks and Discomforts:** The following risks and discomforts are associated with the procedures described above.

*Isometric and isovelocity contractions.* Although we will try to give you enough rest in between contractions, you may develop some muscle fatigue. You may also experience some soreness following the voluntary contractions, which may come about immediately or later in the day. The soreness is normal and will subside in a couple of days. The soreness should not affect your normal daily activities.

*Electrical stimulation.* Although stimulation is brief, you may experience some discomfort.

*Intramuscular Electromyography.* Insertion of the electrode into the muscle will be uncomfortable. However, the discomfort should dissipate after about a minute. If the discomfort persists, slight adjustments can be made to relieve any discomfort. Like any foreign body, the needle electrode poses a risk for infection. This electrode is thoroughly gas-sterilized before it is used. In our experience, no individual has ever experienced adverse consequences from this electrode. It is possible that you may experience nausea, feel faint, and, though extremely rare, lose consciousness. In the event of such experiences, the session will be terminated and all proper measures will be made to ensure your comfort and safety.

*MRI.* When in the magnet, there is a very small possibility that the magnetic field will pull an iron-containing object into the magnet, which might result in physical injury. However, precautions have been taken to prevent such an event from happening; all subjects will walk through a metal detector to ensure that no loose metal objects, like pocketknives or key chains, are brought into the magnet room. If you have a piece of metal in your body, such as fragment in your eye, aneurysm clips, ear implants, spinal nerve stimulators, or a pacemaker, you will not be allowed into the magnet room and cannot participate in this study. One potential hazard of having an MRI is heating of the body due to the radio waves that we use. However, the MRI machine has safety devices that will prevent this from happening. Women, who are pregnant, or trying to conceive, are discouraged from participating in MRI studies due to the potential risks associated with this procedure. Your head will be at the opening of the magnet; however, you may be bothered by feelings of claustrophobia or by the load noise during the MRI session. Temporary hearing loss has been reported from this loud noise, so you will be asked to wear earplugs or headphones. If at any time you feel too claustrophobic or too uncomfortable to continue, the MRI session will be stopped immediately.

**Confidentiality:** Your identity and records will be kept confidential. While results from this study will be shared with other researchers, no individual identities will be used in any reports or publications resulting from this study.

**In Case of Injury:** In the unlikely event of injury, resulting directly from participation in this study, we will do everything we can to assist you in seeking medical treatment.
The University of Massachusetts will not provide compensation for medical treatment you obtain.

**Benefits:** You will receive no direct benefit from participating in this study. Any information that is obtained from this study will be made available to your physician, upon request. The purpose of this study is to provide the investigators with information that will help us understand the mechanisms of muscle weakness in persons with MS. This study may provide an evidence-based rationale for specially-designed exercise therapies improving muscle strength and power in persons with MS.

**Costs and Reimbursement:** You will receive $100 for completing this study. A check will be mailed to your home approximately six weeks after your last visit. In the event that you do not complete the study, partial compensation will be provided as follows: $10 for visit 1 only, $30 each for visits 2, 3, and 4. This study is supported by an ACSM Foundation Research Grant (FRG) from the American College of Sports Medicine Foundation and the National Multiple Sclerosis Society.

**Withdrawal of Participation:** Participation in this research is voluntary. You have the right to withdraw from this study at any time, for any reason.

**Information:** You are encouraged to ask questions about the study. The investigators will attempt to answer all of your questions to the best of their knowledge. The investigators fully intend to conduct the study with your best interest, safety and comfort in mind. Please address any questions regarding the study to Linda Chung, M.S. (413) 545-5305, Dr. Jane Kent-Braun, Ph.D. (413) 545-9477, or Dr. Richard van Emmerik Ph.D. (413) 545-0325. If you would like to speak with someone not directly involved in the research study, you may contact the Human Research Protection Office at the University of Massachusetts via email at humansubject@ora.umass.edu; telephone (413) 545-3428; or mail at the Human Research Protection Office, Research Administration Building, University of Massachusetts Amherst, 70 Butterfield Terrace, Amherst, MA 01003-9242.

<table>
<thead>
<tr>
<th>Participant’s Name</th>
<th>Address</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Signature</th>
<th>Date</th>
<th>Phone Number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Linda Chung, M.S.

Jane Kent-Braun, Ph.D. or Richard van Emmerik, Ph.D.
Medical History Form

Please fill out and sign in ink. This record is confidential.

Name (print):___________________________  Date:__________________

Signature:_________________________________

Medical History
Are you taking any prescribed or over-the-counter medications? Please include vitamins, herbs or other dietary supplements. If yes, please list dose, frequency and duration of use.

______________________________________________________________________
______________________________________________________________________

Have you ever been told by a physician that you should not exercise?  
Yes_____No_____
If yes, please explain:____________________________________________________

______________________________________________________________________
______________________________________________________________________

Do you or have you EVER had any of the following problems? Check if YES and provide details below.

____Heart disease/rheumatic fever  _____Thyroid disorder  _____Asthma
____High blood pressure  _______Claustrophobia  _____Allergies
____Elevated cholesterol  _______Anemia  _____Stroke
____Epilepsy or seizure disorder  _______Diabetes  _____Dizziness
____Blurred or double vision  _______Orthopedic or joint problems (e.g., arthritis)
____Shortness of breath or difficulty in breathing
____Phlebitis, blood clots, varicose veins, peripheral vascular disease

Details:________________________________________________________________
______________________________________________________________________

Lifestyle
Do you smoke cigarettes?  Yes_____  No_____
Do you drink alcohol?  Yes_____  No_____
Do you exercise regularly?  Yes_____  No_____  
If yes, number of times per week_____
Have you had surgery?  Yes_____  No_____  
If yes, when was this?__________________________

Is there any other information or concern you have that you feel we should know about before you participate in the study? If so, please explain.

______________________________________________________________________
PHYSICAL ACTIVITY READINESS QUESTIONNAIRE

1. Has a doctor ever said you have a heart condition and recommended only medically supervised activity?
   Yes____   No____

2. Do you have chest pain brought on by physical activity?
   Yes____   No____

3. Have you developed chest pain in the last month?
   Yes____   No____

4. Do you tend to lose consciousness or fall over as a result of dizziness?
   Yes____   No____

5. Do you have a bone or joint problems that could be aggravated by the proposed physical activity?
   Yes____   No____

6. Has a doctor ever recommended medication for your blood pressure or a heart condition?
   Yes____   No____

7. Are you aware through your own experience, or a doctor’s advice, of any other physical reason against your exercising without medical supervision?
   Yes____   No____

NOTE: If you have a temporary illness, such as a common cold, or are not feeling well at this time – POSTPONE.

NAME___________________________________ DATE________________
<table>
<thead>
<tr>
<th>Condition</th>
<th>Yes</th>
<th>No</th>
<th>Contraindications/Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAA Endovascular Graft</td>
<td>☐</td>
<td>☑</td>
<td>Neurostimulator/TENS Unit</td>
</tr>
<tr>
<td>Anemia/Sickle Cell</td>
<td>☐</td>
<td>☑</td>
<td>Programmable Shunts</td>
</tr>
<tr>
<td>Aneurysm Clip</td>
<td>☐</td>
<td>☑</td>
<td>Prosthesis</td>
</tr>
<tr>
<td>Asthma</td>
<td>☐</td>
<td>☑</td>
<td>Radiation Seeds, Implants</td>
</tr>
<tr>
<td>Bone or Joint Pins</td>
<td>☐</td>
<td>☑</td>
<td>Seizures</td>
</tr>
<tr>
<td>Bone Growth Stimulation</td>
<td>☐</td>
<td>☑</td>
<td>Shrapnel</td>
</tr>
<tr>
<td>Cardiac Pacemaker</td>
<td>☐</td>
<td>☑</td>
<td>Silver Antimicrobial Dressing</td>
</tr>
<tr>
<td>Cochlear/Ear Implant</td>
<td>☐</td>
<td>☑</td>
<td>Stents, Filters or Coils</td>
</tr>
<tr>
<td>Defibrillator (ICD)</td>
<td>☐</td>
<td>☑</td>
<td>Surgery in the past 6 weeks</td>
</tr>
<tr>
<td>Dentures</td>
<td>☐</td>
<td>☑</td>
<td>Swan-Ganz or Thermolitisation Catheter</td>
</tr>
<tr>
<td>Diabetes</td>
<td>☐</td>
<td>☑</td>
<td>Tattoos, Piercings, Permanent Make-up</td>
</tr>
<tr>
<td>Electrodes</td>
<td>☐</td>
<td>☑</td>
<td>Tissue Expander (e.g. breast)</td>
</tr>
<tr>
<td>Electronic Implant or Device</td>
<td>☐</td>
<td>☑</td>
<td>Vascular Access Port and/or Catheter</td>
</tr>
<tr>
<td>Eye Lid Spring or Wire</td>
<td>☐</td>
<td>☑</td>
<td>Other Implants or Devices</td>
</tr>
<tr>
<td>Harrington Rod(s)</td>
<td>☐</td>
<td>☑</td>
<td>Allergies</td>
</tr>
<tr>
<td>Hearing Aids</td>
<td>☐</td>
<td>☑</td>
<td>Gadolinium</td>
</tr>
<tr>
<td>Heart Valve (artificial)</td>
<td>☐</td>
<td>☑</td>
<td>Latex</td>
</tr>
<tr>
<td>Implanted Drug Device</td>
<td>☐</td>
<td>☑</td>
<td>Tape</td>
</tr>
<tr>
<td>Kidney Disease: GFR&lt;30</td>
<td>☐</td>
<td>☑</td>
<td>Previous Contrast Dye</td>
</tr>
<tr>
<td>Magnetically Activated Device</td>
<td>☐</td>
<td>☑</td>
<td>Women Only</td>
</tr>
<tr>
<td>Medication Pump</td>
<td>☐</td>
<td>☑</td>
<td>IUD</td>
</tr>
<tr>
<td>Metal Fragments in Eyes-Ears-Ever</td>
<td>☐</td>
<td>☑</td>
<td>Breastfeeding</td>
</tr>
<tr>
<td>Medication Patch</td>
<td>☐</td>
<td>☑</td>
<td>Pregnancy</td>
</tr>
</tbody>
</table>

I attest that I have been informed and am aware of the risks and benefits as well as alternatives. I have had the opportunity to ask questions, and any questions I have asked have been answered to my satisfaction. I attest to the accuracy of the information I have provided. I voluntarily consent to this scan/procedures(s).

<table>
<thead>
<tr>
<th>Signature of Patient</th>
<th>Date</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signature of Witness (if applicable)</td>
<td>Date</td>
<td>Time</td>
</tr>
<tr>
<td>Signature of MRI Technologist</td>
<td>Date</td>
<td>Time</td>
</tr>
<tr>
<td>Signature of Translator (if applicable)</td>
<td>Date</td>
<td>Time</td>
</tr>
</tbody>
</table>

If the patient is incompetent because of physical or mental condition or is a minor, complete:
Patient is a minor ______ years of age or is unable to give consent because:

Authorized Agent / Relationship | Date | Time | am / pm

Page 2 of 2
Patient Administered
*Expanded Disability Status Scale*
*EDSS*®

University of Washington

Department of Neurology
Multiple Sclerosis Research Center

Developed for research purposes in Multiple Sclerosis  (1999)
**We would like to know how well your body functions on an average day, not your worst days and not your best days. Please check the box that most closely matches your abilities.**

**Walking distances:** On an average day I can:

1. ☐ Walk more than 3 tenths of a mile without stopping to rest.  
   (This is a little further than 5 football field lengths.)
   I would need ☐ no help ☐ a cane ☐ two canes ☐ a walker

2. ☐ Walk 2 tenths of a mile without stopping to rest.  
   (This is a little further than 3 football field lengths.)
   I would need ☐ no help ☐ a cane ☐ two canes ☐ a walker

3. ☐ Walk 600 feet without stopping to rest.  
   (This is 2 football field lengths.)
   I would need ☐ No help ☐ A cane ☐ Two canes ☐ A walker

4. ☐ Walk 300 feet without stopping to rest.  
   (This is 1 football field length.)
   I would need ☐ No help ☐ A cane ☐ Two canes ☐ A walker

5. ☐ Walk 60 feet without stopping to rest.
   I would need ☐ No help ☐ A cane ☐ Two canes ☐ A walker

6. ☐ Walk 15 feet without stopping to rest
   I would need ☐ No help ☐ A cane ☐ Two canes ☐ A walker

7. ☐ Walk a few steps.
   I would need ☐ No help ☐ A cane ☐ Two canes ☐ A walker

8. ☐ Use a wheelchair
If you use a wheelchair please check one of the following 4 statements:

1. □ On an average day, I can bear my weight with my legs (stand up and move) and get myself from one chair to another.

2. □ On an average day, I can bear my weight (with the strength in my arms) and lift myself from one chair to another.

3. □ On an average day, I cannot bear any weight or get myself from one chair to another.

4. □ On an average day, I cannot sit up in a chair.

**When answering the following questions, please think about an average day for you (not a particularly good, or bad day) then think of the “best” part of that day. (Maybe the best part of your day is in the morning, or maybe later, after you have moved around a bit.)**

**Strength:**

On an average day, at my best, my strength is:

<table>
<thead>
<tr>
<th></th>
<th>The same as before I had MS</th>
<th>Almost the same as before I had MS</th>
<th>Can barely raise limb in the air</th>
<th>Can move limb, but not raise it in the air</th>
<th>Cannot move limb at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right arm</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Left arm</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Right leg</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Left leg</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>
**Coordination:**

On an **average** day, **at my best**, my coordination:

<table>
<thead>
<tr>
<th></th>
<th>The same as before I had MS</th>
<th>Almost the same as before I had MS</th>
<th>Interferes with some movements, though I can eventually complete them without help</th>
<th>I must get help, use a mechanical device, or brace the limb to complete movements</th>
<th>Prevents me from completing movements even with help.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right arm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left arm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right leg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left leg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Sensation:**

**For touch, pain, cold, or heat, please mark the appropriate box in the table below. Use the worst – the one that has lost the most sensitivity – of the four sensations (touch, pain, cold, or heat) to answer each question. Please think of an average day.**

*(For example: your left hand has very little sensitivity to pain, mild sensitivity to touch, and normal for heat and cold, then you would mark “can feel very little” on the line for left hand.)*

<table>
<thead>
<tr>
<th></th>
<th>Same as before I had MS</th>
<th>Mild loss of sensation</th>
<th>Moderate loss of sensation</th>
<th>Can feel very little</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right hand</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right arm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left hand</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left arm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left hand</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right foot</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right leg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left foot</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left leg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Bladder:**

154
On an average day, I have:

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>
| ☐   | ☐  | A normal bladder
| ☐   | ☐  | Urgency (once I need to go I have a hard time holding it)
| ☐   | ☐  | Hesitancy (I feel I need to go but nothing happens)
| ☐   | ☐  | Accidents (incontinence) occasionally but once a week or less
| ☐   | ☐  | Accidents (incontinence) twice a week or more, but less than daily
| ☐   | ☐  | Accidents (incontinence) daily
| ☐   | ☐  | Use self catheterization
| ☐   | ☐  | Use continuous catheter (indwelling or condom catheter)

Vision:

1. Which line is the smallest that you can read (you can use glasses if needed).

<table>
<thead>
<tr>
<th>Left eye only</th>
<th>Right eye only</th>
<th>Both eyes together</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>☐</td>
<td>☐</td>
<td>☐</td>
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<tr>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

2. I see double (two things, where there is really only one):

☐ Never  ☐ About once a week  ☐ Almost daily  ☐ Constantly

3. On an average day, my eye movements are unsteady
☐ Never ☐ Only when looking to the side ☐ All the time

**Speech:**

On an average day, my speech is:

☐ Is the same as before I had MS
☐ Slightly Slurred
☐ Moderately Slurred
☐ Severely Slurred

**Swallowing:**

On an average day, my swallowing is:

☐ Normal
☐ Occasional choking
☐ Unable to swallow

**Thinking:**

On an average day, my thinking and memory is:

**Although some people may wish to consider thinking and memory separately, we need you to combine them and check one box below.**

☐ Is the same as before I had MS
☐ Is almost the same as before I had MS
☐ Occasionally causes a problem in my daily life
☐ Frequently causes a problem in my daily life
☐ Others have to help me manage my affairs

Check only one box that best describes your MS disease activity over time
☐ Attacks (exacerbations, relapses) come on over a few hours or days, last from one day to several weeks, but once they are over, you feel the same as you always have.

☐ Attacks (exacerbations, relapses) come on over a few hours or days, last from one day to several weeks. After some attacks, your symptoms are worse than before. The symptoms that remain after the attack are stable until a new attack occurs.

☐ At the start of the disease, attacks (exacerbations, relapses) occur. You may feel your symptoms get worse because of these attacks. Then even between the attacks, you feel you are getting worse. In some cases, attacks cease yet your symptoms continued to worsen.

☐ Symptoms worsen from the beginning. Your symptoms may be stable for a time, gradually worsen, or deteriorate rapidly, but attacks (exacerbations, relapses) have never occurred.

☐ Symptoms gradually worsen from the beginning. Your symptoms may be stable for a time at the beginning, or may deteriorate rapidly. Attacks (exacerbations, relapses) did not occur at the start, but may occur later in the course of the disease.
MODIFIED FATIGUE IMPACT SCALE (MFIS)

Following is a list of statements that describe how fatigue may affect a person. Fatigue is a feeling of physical tiredness and lack of energy that many people experience from time to time. In medical conditions like MS, feelings of fatigue can occur more often and have a greater impact than usual. Please read each statement carefully, and then circle the one number that best indicates how often fatigue has affected you in this way during the past 4 weeks. (If you need help in marking your responses, tell the interviewer the number of the best response.) Please answer every question. If you are not sure which answer to select, please choose the one answer that comes closest to describing you. The interviewer can explain any words or phrases that you do not understand.

Because of my fatigue during the past 4 weeks....

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I have been less alert.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. I have had difficulty paying attention for long periods of time.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. I have been unable to think clearly.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. I have been clumsy and uncoordinated.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. I have been forgetful.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. I have had to pace myself in my physical activities.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. I have been less motivated to do anything that requires physical effort.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Because of my fatigue during the past 4 weeks....

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>8.</td>
<td>I have been less motivated to participate in social activities.</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>9.</td>
<td>I have been limited in my ability to do things away from home.</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>10.</td>
<td>I have had trouble maintaining physical effort for long periods.</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>11.</td>
<td>I have had difficulty making decisions.</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>12.</td>
<td>I have been less motivated to do anything that requires thinking.</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>13.</td>
<td>My muscles have felt weak.</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>14.</td>
<td>I have been physically uncomfortable.</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>15.</td>
<td>I have had trouble finishing tasks that require thinking.</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>16.</td>
<td>I have had difficulty organizing my thoughts when doing things at home or at work.</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>17.</td>
<td>I have been less able to complete tasks that require physical effort.</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>18.</td>
<td>My thinking has been slowed down.</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>19.</td>
<td>I have had trouble concentrating.</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
Because of my fatigue during the past 4 weeks:

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td>20. I have limited my physical activities.</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<tr>
<td>21. I have needed to rest more often or for longer periods.</td>
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<tr>
<td></td>
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<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Fatigue Severity Scale

Below are a series of statements regarding your fatigue. By fatigue we mean a sense of tiredness, lack of energy or total body give-out. Please choose a number from 1 to 7 the best indicates your degree of agreement or disagreement with the statement. Please answer these questions as they apply to the past TWO WEEKS.

<table>
<thead>
<tr>
<th>Statement:</th>
<th>Strongly disagree</th>
<th>Strongly agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. My motivation is lower when I am fatigued.</td>
<td>1  2  3  4  5  6  7</td>
<td></td>
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<tr>
<td>2. Exercise brings on my fatigue.</td>
<td>1  2  3  4  5  6  7</td>
<td></td>
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<tr>
<td>3. I am easily fatigued.</td>
<td>1  2  3  4  5  6  7</td>
<td></td>
</tr>
<tr>
<td>4. Fatigue interferes with my physical functioning.</td>
<td>1  2  3  4  5  6  7</td>
<td></td>
</tr>
<tr>
<td>5. Fatigue causes frequent problems for me.</td>
<td>1  2  3  4  5  6  7</td>
<td></td>
</tr>
<tr>
<td>6. My fatigue prevents sustained physical functioning.</td>
<td>1  2  3  4  5  6  7</td>
<td></td>
</tr>
<tr>
<td>7. Fatigue interferes with carrying out certain duties and responsibilities.</td>
<td>1  2  3  4  5  6  7</td>
<td></td>
</tr>
<tr>
<td>8. Fatigue is among my most three disabling symptoms.</td>
<td>1  2  3  4  5  6  7</td>
<td></td>
</tr>
<tr>
<td>9. Fatigue interferes with my work, family or social life.</td>
<td>1  2  3  4  5  6  7</td>
<td></td>
</tr>
</tbody>
</table>
Anthropometrics & Blood pressure

Height (in)______ Weight (lbs)______ knee-ankle length (cm): left______ right______

Seated BP_______ hip-knee length (cm): left______ right______

Physical Function

5x chair rises (s)____

25ft walk speed (s) – Trial 1: usual____ brisk____ Trial 2: usual____ brisk____

10s foot-tap (counts) – Trial 1: left____ right____ Trial 2: left____ right____

☐ Energy Cost of Walking protocol  ☐ Questionnaires

Biodex Dynamometer - Habituation

Dominant leg (circle one): left right  Good leg (no weakness/no spasticity): left right

Seat____ DynHeight____ Knee Attachment: ______ Sampling rate (Hz): ______

Left total ROM____ left KE_MVIC (90deg): 1)_____ 2)_____ 3)_____ 4)_____

Right total ROM____ right KE_MVIC (90deg): 1)_____ 2)_____ 3)_____ 4)_____

(circle one) left right KE_MVIC (90deg): 1)_____ 2)_____ 3)_____ 4)_____

☐ ROM set at 70deg, starting at 90deg

Passive protocol: ☐ 10dps  ☐ 60dps  ☐ 120dps  ☐ 180dps  ☐ 240dps  ☐ 300dps

MVDC protocol: ☐ 30dps  ☐ 60dps  ☐ 120dps  ☐ 180dps  ☐ 240dps  ☐ 300dps

Comments:

☐ Actigraph #_______________  ☐ Activity Log (30s epoch)  Date given: __________
Visual Analog Fatigue Scale

*Draw a vertical line on the scale that best represents your overall sense of fatigue.*

No fatigue | Severe fatigue
Spasticity Scale (Rizzo et al. 2004)

*Please circle the number next to the statement that corresponds to your level of spasticity.*

0. I have no symptoms of spasticity.

1. I notice some problems with spasticity, but they do not interfere with my activities.

2. Spasticity occasionally forces me to change some of my activities, e.g., once a week or less.

3. Spasticity frequently affects some of my activities, e.g., several times a week.

4. Every day, spasticity problems force me to modify my daily activities.

5. Every day, spasticity problems prevent me from doing many of my daily activities.

---

Visual Analog Scale for spasticity

*Draw a vertical line on the scale that best represents your level of spasticity in your left leg.*

![Left Leg Scale](image1)

No spasticity | Severe spasticity

*Draw a vertical line on the scale that best represents your level of spasticity in your right leg.*

![Right Leg Scale](image2)

No spasticity | Severe spasticity
Activity Log

Please fill out this log completely during the period that you are wearing the monitor. It is important that you fill this log out daily so that you do not forget any events. If you have any questions please feel free to contact the Muscle Physiology Laboratory at 545-5305.

There is additional room on the back pages if you need more space.

Day 1

Date: __________

Wake up Time: ________________ Bed Time: ________________

Please list any physical activities (such as long walks, yard work, fitness club, etc), as well as any naps during the day:

<table>
<thead>
<tr>
<th>Activity</th>
<th>Time</th>
<th>Duration</th>
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<tbody>
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</tbody>
</table>

Was the monitor worn during all waking hours (except for showering)?

☐ Yes  ☐ No, Times not worn: ____________________________

Was there anything out of the ordinary about your activity pattern this day?

☐ Yes, Explain Below  ☐ No
Day 2

Wake up Time: ________________  Bed Time: ________________

Please list any physical activities (such as long walks, yard work, fitness club, etc), as well as any naps during the day:
Activity:  Time:  Duration

________________________________________________________
________________________________________________________
________________________________________________________

Was the monitor worn during all waking hours (except for showering)?
□ Yes  □ No, Times not worn: ________________________________

Was there anything out of the ordinary about your activity pattern this day?
□ Yes, Explain Below  □ No

Day 3

Wake up Time: ________________  Bed Time: ________________

Please list any physical activities (such as long walks, yard work, fitness club, etc), as well as any naps during the day:
Activity:  Time:  Duration

________________________________________________________
________________________________________________________
________________________________________________________

Was the monitor worn during all waking hours (except for showering)?
□ Yes  □ No, Times not worn: ________________________________

Was there anything out of the ordinary about your activity pattern this day?
□ Yes, Explain Below  □ No
Day 4

Wake up Time: ____________  Bed Time: ____________

Please list any physical activities (such as long walks, yard work, fitness club, etc), as well as any naps during the day:

<table>
<thead>
<tr>
<th>Activity</th>
<th>Time</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

Was the monitor worn during all waking hours (except for showering)?

☐ Yes  ☐ No, Times not worn: ________________________

Was there anything out of the ordinary about your activity pattern this day?

☐ Yes, Explain Below  ☐ No

Day 5

Wake up Time: ____________  Bed Time: ____________

Please list any physical activities (such as long walks, yard work, fitness club, etc), as well as any naps during the day:

<table>
<thead>
<tr>
<th>Activity</th>
<th>Time</th>
<th>Duration</th>
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<tbody>
<tr>
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</tbody>
</table>

Was the monitor worn during all waking hours (except for showering)?

☐ Yes  ☐ No, Times not worn: ________________________

Was there anything out of the ordinary about your activity pattern this day?

☐ Yes, Explain Below  ☐ No
**Day 6**
Date: ____________

Wake up Time: ____________  Bed Time: ____________

Please list any physical activities (such as long walks, yard work, fitness club, etc), as well as any naps during the day:
<table>
<thead>
<tr>
<th>Activity</th>
<th>Time</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

Was the monitor worn during all waking hours (except for showering)?

☐ Yes  ☐ No, Times not worn: ____________________________

Was there anything out of the ordinary about your activity pattern this day?

☐ Yes, Explain Below  ☐ No

---

**Day 7**
Date: ____________

Wake up Time: ____________  Bed Time: ____________

Please list any physical activities (such as long walks, yard work, fitness club, etc), as well as any naps during the day:
<table>
<thead>
<tr>
<th>Activity</th>
<th>Time</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

Was the monitor worn during all waking hours (except for showering)?

☐ Yes  ☐ No, Times not worn: ____________________________

Was there anything out of the ordinary about your activity pattern this day?

☐ Yes, Explain Below  ☐ No
Day 8  

Date: ____________

Wake up Time: _______________  Bed Time: _______________

Please list any physical activities (such as long walks, yard work, fitness club, etc), as well as any naps during the day:

Activity:  Time:  Duration

Was the monitor worn during all waking hours (except for showering)?

☐ Yes  ☐ No, Times not worn: __________________________

Was there anything out of the ordinary about your activity pattern this day?

☐ Yes, Explain Below  ☐ No

Day 9  

Date: ____________

Wake up Time: _______________  Bed Time: _______________

Please list any physical activities (such as long walks, yard work, fitness club, etc), as well as any naps during the day:

Activity:  Time:  Duration

Was the monitor worn during all waking hours (except for showering)?

☐ Yes  ☐ No, Times not worn: __________________________

Was there anything out of the ordinary about your activity pattern this day?

☐ Yes, Explain Below  ☐ No
Day 10

Date: 

Wake up Time: 

Bed Time: 

Please list any physical activities (such as long walks, yard work, fitness club, etc), as well as any naps during the day:

<table>
<thead>
<tr>
<th>Activity:</th>
<th>Time:</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>

Was the monitor worn during all waking hours (except for showering)?

☐ Yes

☐ No. Times not worn: 

Was there anything out of the ordinary about your activity pattern this day?

☐ Yes, Explain Below

☐ No

Comments & Additional Space (please include date to which comment belongs):


39. **Forth KE, Metter EJ and Paloski WH.** Age associated differences in postural equilibrium control: a comparison between EQscore and minimum time to contact (TTC(min)). *Gait Posture* 25: 56-62, 2007.


