Spring 5-7-2016

Mobility of Individuals with Multiple Sclerosis and the Influence of Physical Therapy

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Recommended Citation

Davies, Brenda L., "Mobility of Individuals with Multiple Sclerosis and the Influence of Physical Therapy" (2016). *Theses & Dissertations*. 70.
https://digitalcommons.unmc.edu/etd/70

MOBILITY OF INDIVIDUALS WITH MULTIPLE SCLEROSIS AND THE INFLUENCE OF PHYSICAL THERAPY

by

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Presented to the Faculty of

the University of Nebraska Graduate College

in Partial Fulfillment of the Requirements

for the Degree of Doctor of Philosophy

Medical Sciences Interdepartmental Area
Graduate Program

(Munroe-Meyer Institute)

Under the Supervision of Professor Max J. Kurz

University of Nebraska Medical Center
Omaha, Nebraska

April, 2016

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ACKNOWLEDGEMENTS

First of all I want to say thank you to everyone who dedicated their own time to assisting me with the projects that were completed for my dissertation. A special thanks goes out to the wonderful physical therapists who helped with the therapeutic interventions – Kathy Volkman, Heidi Reelfs, Brad Corr, and Reggie Harbourne. Also, to the many PT students who helped assist the PTs with the therapy sessions – y'all were a major help too! Next I want to thank the many students who helped me with the numerous data collections – Dave Arpin, Min Liu, Rashelle Hoffman, and Jamie Gehringer. Thank you so much for all the times you didn't mind putting your own work down to help me out! I also want to thank the clinicians who helped me recruit subjects to my many studies – Drs. Rana Zabad and Kathi Healey.

I also want to acknowledge my family and tell them thanks! I couldn't have done it without any of y'all sitting there encouraging me every step of the way. There's too many of you to mention by name but you know who you are.

Next – I want to thank my committee members for providing feedback and encouragement along the way as well. I learned from you all every single time we got together and am so thankful you were there.

Finally, I want to say a huge thanks to Max! I couldn't have completed anything without your guidance. Your door was always open and I know there were days I'm sure you didn't want to hear another question from me. Thank you for being there and helping me out all along the way.

MOBILITY OF INDIVIDUALS WITH MULTIPLE SCLEROSIS AND THE INFLUENCE OF PHYSICAL THERAPY

Brenda L. Davies, Ph.D.

University of Nebraska, 2016

Supervisor: Max J. Kurz, Ph.D.

One main purpose was to explore the compensatory gait strategies of individuals with multiple sclerosis (MS). To address this purpose, we quantified the mechanical work generated by the lower extremity joints during walking. The outcomes from this investigation suggested that individuals with MS redistribute positive mechanical work during walking to the hip in order to compensate for a reduced ability of the ankle to generate positive mechanical work. Additionally, we also explored the motor control of the ankle as a potential contributing factor to the mobility limitations of individuals with MS. The outcomes from this investigation indicated that individuals with MS have reduced ankle control, which is related to the reductions in walking ability. These results suggest that poor ankle motor control may be a limiting factor to the mobility of individuals with MS.

Another main purpose was to evaluate whether novel physical therapy interventions could promote improvements in the postural control and mobility of individuals with MS. The first therapeutic intervention specifically targeted the ankle musculature with motor adaptation exercises. After completion of this program, our subjects with MS displayed clinically relevant improvements in their postural balance and mobility as well as improved ankle motor control, which was related to the improved postural balance. The second therapeutic intervention sought to interrogate whether these improvements were influenced by the type of activities performed or the unusually high dosage at which they were performed. The outcomes from this investigation found that both types of therapeutic interventions promoted similar improvements in the balance and mobility of individuals with MS. Moreover, the second therapeutic intervention promoted improvements in the control of trunk accelerations during walking. These results suggest that potentially the level of activity is more important than the type of activities being performed to attaining clinically relevant improvements. Altogether this dissertation provides novel information about the compensatory gait strategies of individuals with MS and the influence of therapeutic interventions upon these strategies. Both will be useful for the development of superior treatment options for these individuals.

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LIST OF ABBREVIATIONS

AFO	ankle foot orthosis
BC	Bradley Corr
CV	coefficient of variation
EDSS	Kurtzke Expanded Disability Status Score
HR	Heidi Reelfs
KV	Kathleen Volkman
MAC	motor adaptation cohort
MAS	Modified Ashworth Scale
MS	multiple sclerosis
MVT	maximal voluntary torque
PF	plantarflexors
RH	Rashelle Hoffman
RMS	root mean square
RR	relapsing-remitting
SampEn	Sample Entropy
SD	standard deviation
SEM	standard error of the mean
SOT	sensory organization test
SP	secondary progressive

TEC	therapeutic exercise cohort
UNMC	University of Nebraska Medical Center

INTRODUCTION

Multiple Sclerosis

Multiple sclerosis (MS) is an inflammatory demyelinating disease that affects individuals between the ages of 20-65 years old.[76] Currently about 570,000 individuals in the United States have a diagnosis of MS and it is about two to three times more common in females than males.[14,76] There are four forms of MS: relapsing-remitting, secondary progressive, primary progressive, and progressive relapsing. The relapsing-remitting form of the disease is characterized by the presence of acute neurological symptoms followed by partial or complete remission. Relapsing-remitting MS may become progressive in nature and characterized by the occurrence of demyelination, axonal loss, and gliosis. This progressive phase is known as secondary progressive MS. A minimal number of individuals with MS are faced with progressive MS symptoms from disease onset with no relapsing-remitting phase of the disease; this presentation of MS is known as primary progressive MS. Currently MS is one of the most common contributors of neurologic disability for young and middle aged adults.[31,115] Because of the demyelination and inflammation that occurs with MS, individuals with MS face a large amount of disability and impairments. Some common symptoms of MS include gait deficits, balance impairments, increased fatigue levels, weak and/or spastic muscles, dizziness, and depression. However, the amount and type of disability is heterogeneous and varies greatly among patients.

Balance and Walking

Proper balance is vital for upright posture and control, especially during walking. Stable balance is dependent upon the accurate integration and interpretation of the visual, somatosensory, and vestibular cues. Impairments in any one of these three systems can result in impaired balance. Individuals with MS typically display a higher amount of sway in their center of pressure patterns during quiet standing than healthy adults and this amount of sway tends to increase with the removal of vision.[16,109,118] Additionally, individuals with MS have reduced limits of stability.[77] During quiet standing, individuals with MS display long postural latencies when responding to perturbations.[13,70] Moreover, individuals with MS perform worse in functional reach tests during quiet standing than healthy adults.[97] These individuals also have a reduction in the temporal variations of the center of pressure time series, which is assumed to represent a less adaptable or more rigid postural sway.[64] The increased amount of postural sway and decreased limits of stability have been related to an increased occurrence of falling.[79]

Walking ability has been rated as one of the most important functional abilities to individuals with MS.[58] About 52% of individuals with MS report falling at least once within the past six months and about 50% of individuals with MS will become reliant upon an assistive device for ambulation within their lifetime.[48,149] It is well known that individuals with MS take shorter step lengths and walk at slower speeds and cadences than healthy adults.[5,74,81,97] Additionally, these individuals spend more time in double support. Recent investigations have found that individuals with MS display reduced moments and limited range of motion during walking, especially at the ankle.[63,81,97] It has been suggested that these alterations in the gait patterns of individuals with MS may contribute to a higher metabolic cost of walking for individuals with MS.[105,114]

In addition to altered gait patterns, individuals with MS have altered amounts and structure of variability in their walking patterns, which may lead to more unstable walking. Individuals with MS tend to have more variable step timing, step lengths and widths, and a more variable percentage of time spent in double or single support.[132,133,136] Individuals with MS also have greater joint angle variability at the lower limb joints than healthy adults.[32] Recent investigations have found that individuals with MS have a less periodic structure to the trunk acceleration variability.[61] It has also been found that individuals with MS have more regular and repeatable step length and step width patterns, suggesting that these individuals are unable to adapt their walking patterns to meet unforeseen changes in the constraints of the task.[72] Therefore, potentially individuals with MS have altered amounts and structure of variability present during gait which may suggest these individuals employ different control strategies than healthy adults. It has been postulated that many of the alterations in the gait patterns of individuals with MS, especially the changes in spatiotemporal parameters of gait, are compensatory strategies these individuals adopt because of compromised stability during walking, which may be due to the altered variability present.

Stabilization of the trunk during walking is vital to achieving dynamic balance and also stabilization of the head. The trunk is an important control aspect of walking because it contains about 2/3 of the body's weight and is located at about 2/3 of the body's height from the ground.[155] Proper integration of the accelerations, position, and velocity of the trunk by the somatosensory and vestibular system are vital for maintenance of stability and gait execution.[65,101,103] Accelerometry has been used to explore the gait of healthy adults, the elderly, and numerous clinical populations; the amount of variability within these acceleration patterns have been able to provide insight into the control mechanisms underlying gait alterations in these populations.[41,66,67,80,96,98,102] Recently, a small number of investigations have explored the trunk accelerations of individuals with MS during walking using both linear and non-linear techniques to quantify variability.[59,61,138] Huisinga et al.[61] used the combination of linear techniques, such as root mean square, and non-linear techniques, such as Lyapunov exponents, to explore the variability in the mediolateral and antero-posterior acceleration directions during a 30 second walk by both healthy adults and individuals with MS. The individuals with MS displayed normal or lower amounts of variability in the both directions, but had more divergence in both directions, suggesting that the trunk acceleration patterns of individuals with MS are less periodic. Less periodic and more divergent patterns may indicate a lower amount of stability and have been related to an increased risk of falling. Potentially, the trunk acceleration variability contributes to the compensatory strategies adopted by individuals with MS during walking.

Human walking has often been described using an inverted pendulum model.[18] In this model, the body’s center of mass travels in an arch trajectory. At the end of this arch trajectory for one leg, the pendulum transfers to the other leg which proceeds in a similar manner. At this step-to-step transition point, the center of mass must be redirected which requires mechanical work in order for a human to maintain a steady walking speed.[43] Positive mechanical work occurs when mechanical energy is generated and contributes to propelling the body forward. Negative mechanical work occurs when mechanical energy is dissipated or absorbed by a joint. During the stance phase of gait, positive and negative work is distributed across the ankle, knee, and hip joints. The ankle joint produces the majority of positive work during the stance phase, especially late stance, and the knee joint typically produces negative work.[145] Both positive and negative mechanical work are generated by the hip joint but the positive work generally outweighs the negative work.[145]

Previous investigations have shown that elderly and clinical populations tend to redistribute the mechanical work across the joints in order to compensate for decreases in muscle strength, the inability to generate rapid torque, and limited range of motion about a joint.[39,71,99,108] A common redistribution pattern that occurs in order to compensate for the reduced positive work produced by the ankle joint is that the hip joint generates an increased amount of work. It has been suggested that this redistribution to a hip joint strategy substantially increases the metabolic energy expenditure during walking because a hip strategy is unable to rely upon the metabolic free elastic energy provided by the Achilles tendon during gait.[125] It is possible that individuals with MS may adopt a hip compensatory strategy during gait due to the limited amount of mechanical work generated by the ankle joint. Although this conjecture seems plausible, currently there is limited insight on how MS impacts the mechanical work produced by the lower extremity joints during walking.

Motor Control and the Ankle Musculature

The walking and balance deficits seen in individuals with MS may be caused by the impairments in the sensorimotor system that occur with the disease. Potentially, slowed conduction of somatosensory and proprioceptive cues contributes to the deficits in the balance and mobility of individuals with MS.[13] Also, the presence of a higher amount of variability within the movements of individuals with MS suggests there may be an increase in noise within the neuromuscular system. These increases in noise may partially be due to the alterations in the composition and control of the musculature of individuals with MS. Individuals with MS often display high amounts of muscle weakness, muscle spasticity, a lower capacity for muscle activation, increased muscle fatigue, and latent muscular activity.[13,20,74,90,116,120,126,134,139,140,147] Additionally, individuals with MS display asymmetry in the strength and utilization of their legs during walking and balance, suggesting that the neuromuscular control to one leg is altered more than the other.[13,29,79] It has been suggested that the neuromuscular impairments at the ankle have devastating effects upon the mobility and balance of individuals with MS.[13,63,134,147] Previous investigations have specifically cited the muscle weakness, spasticity, and muscle recruitment patterns at the ankle as direct contributors to the slower walking speeds seen in people with MS.[134,147] These neuromuscular alterations may be a contributing factor to reduced power generation, which is thought to be a predictor of step length and walking velocity.[63,81,97]

Another potential limiting factor contributing to the balance and mobility deficits of individuals with MS could be reduced motor control of the ankle musculature. Motor control is vital to proper execution of human movement and it can be defined as the ability to regulate or direct the mechanisms essential to movement.[130] By studying motor control, we can gain an understanding of the central organization and state of the nervous system underlying the motor output. Coordinated human movements are reflective of proper motor control and integration of the sensory information needed to perform a motor task. With this coordination, humans often display fairly regular and repeatable movement patterns. However, it is common for movements to be slightly variable in terms of the kinematics, kinetics, and muscle activation patterns. By quantifying and exploring the amount of variability in a movement, we can gain knowledge about the motor control that underlies the movement.

Scientists have often used continuous or dynamic isometric force contractions to explore the motor control of the upper and lower extremities. During a continuous isometric motor task, subjects attempt to generate and sustain a force that matches a static target force value, while for a dynamic isometric task subjects attempt to ramp up and down their isometric force production to match a target force that often has a parabolic shape. The force exerted during both these types of contractions will typically fluctuate around an average force value. While it is normal to have a small amount of variability in these isometric contractions, too much or too little variability suggests faulty motor control strategies. If an individual displays an altered amount of variability in their force patterns, one's coordination in daily activities can be hindered. Due to the major role the lower extremities play in daily living, the motor control of the legs has been studied extensively, especially in an aged population.

Elderly individuals have a high risk of falling; therefore, previous investigations have sought to determine whether this is influenced by the motor control of the lower extremities. Previous investigations have shown that older adults have impaired steadiness during both submaximal continuous (Figure 1) and dynamic isometric motor tasks.[11,21,22,27,45,83,86,89,143] This variability in a motor task has been found to be influenced by the velocity of the movement or the contraction type being performed.[22,24] It has been proposed that these decreases in the motor control of the lower extremities are due to neurophysiological alterations (i.e., decreased motor unit discharge rate) which occur with aging at both the higher control centers and at the muscle level.

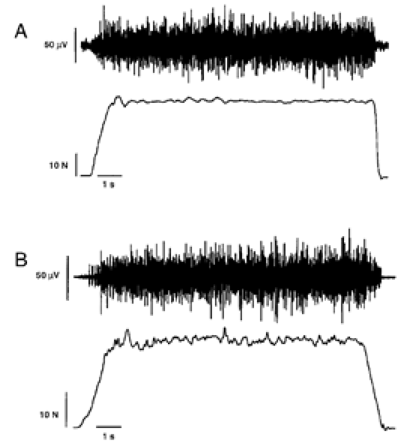

Figure 1: Representative Continuous Isometric Motor Task Data. Representative data from an isometric constant-force trial performed at 10% maximal voluntary contraction (MVC) in young (A) and old (B) subject. *Top traces:* vastus lateralis (VL) interference electromyogram (EMG). *Bottom traces:* knee extensor force.[143]

Previous investigations have found that the amount of variability present in a low-level continuous contraction force pattern is related to the amount of postural sway during quiet standing.[86,100] This relationship suggests that an individual with reduced motor control at the ankle, as represented by a higher amount of variability, will more than likely have decreased postural stability. While isometric ankle force control during a continuous motor task has been seen to be related to postural stability, previous investigations have struggled to find a relationship between this type of contraction and functional abilities such as walking or climbing stairs.[15,95,129] Potentially this is due to the degree of similarity between the motor tasks being explored in such experiments. The low-level continuous isometric contraction tasks employed in previous investigations are relatively similar to quiet standing in terms of the motor control strategies and muscle activation properties but the motor control during functional tasks is more dynamic in nature than continuous isometric motor tasks and the muscle activation is different. Thus, the use of a low-level dynamic force task may be more useful in identifying the motor control deficits of the ankle musculature that potentially limit functional tasks such as walking.

Despite the recognition of the importance of motor control and the altered amount of motor control in clinical populations, the motor control of the lower extremities of individuals with MS has not been well explored. Previous investigations have utilized isokinetic and isometric contraction tasks to quantify and better understand the neuromuscular alterations that occur with MS.[13,20,74,90,116,120,126,139,140] However, the amount of variability present in the force generation patterns in these types of activities have not been well explored in individuals with MS. Previous electroencephalography investigations have suggested that the damage to the central nervous system caused by MS may impact the cortical activations associated with the production of motor actions.[93,94] Additionally, transcranial magnetic stimulation studies have shown slowed transmission of the motor command along the corticospinal tract, which would result in altered movement patterns.[50,73] Individuals with MS also have slowed somatosensory conduction which may influence the rate at which information can be received and processed for proper execution of a motor task.[13] Therefore, these alterations in the neuromuscular system may contribute to a decrease in motor control, which in turn may limit the postural balance and mobility of individuals with MS. By quantifying the motor control during isometric motor tasks, we may be able to gain valuable insight into the neuromuscular deficits that significantly impact the functional ability of individuals with MS. Additionally, we may also be able to relate the alterations in motor control to the deficits present in the walking and balance of individuals with MS.

Therapeutic Interventions

Since balance and walking are so vital for completion of daily activities, these are two areas commonly targeted with physical therapy interventions for individuals with MS. However, traditionally clinicians discouraged individuals with MS from participating in physical activity or intensive physical therapy interventions.[34,122,141] This was due to the belief that physical activity would exacerbate the MS symptoms, such as causing excessive fatigue or increasing sensory symptoms.[34,122,131,141] Also, by not participating in physical activity, individuals with MS would be able to preserve more energy for completing daily physical activities. However, this traditional way of thinking has been challenged recently and a number of clinical investigations have found beneficial outcomes on the balance and mobility of individuals with MS following exercise or active physical therapy protocols. These previous investigations have explored the influence of many different therapeutic and exercise modalities including resistance training, balance training, walking or aerobic training, and even more novel techniques.

Resistance training programs have been used with individuals with MS because of the potential to increase muscle strength, which is significantly reduced in these individuals. These programs typically meet 2-3 times per week for 30-60 minutes over a 3-12 week period. Despite usually promoting increases in the muscle strength of individuals with MS, the influence of these types of programs on other MS symptoms have been fairly inconclusive.[10,35,42,47,54,137,142,151] Some of these previous investigations have found that progressive resistance training can significantly improve the spatiotemporal kinematics of gait and perceived fatigue levels.[54,104,142,151] However, many found no influence upon balance or mobility.[10,38,42] Thus, while resistance training has been beneficial to increasing the muscle strength of individuals with MS, it may not be beneficial to improving the overall functional ability of these individuals.

Aerobic activities, such as treadmill walking, have been a large focus of the current literature because of its direct relationship to the mobility impairments seen in individuals with MS.[7,52,60,62,111] These programs typically meet 2-3 times per week for 30 minutes over a 4-12 week period. The outcomes of such activities have had mixed results with some simply reporting no adverse events or no increases in fatigue levels, while others have reported improvements in walking speed, endurance, and the amount of torque or power generated by the ankle and hip during gait.[7,52,62,111] A recent investigation also explored the influence of combining various types of aerobic activities such as aquatic therapy and aerobic training together with traditional physical therapy.[75] Participants from this program displayed improvements in their walking ability following completion of the program. Therefore, while these types of programs do not appear to be detrimental to individuals with MS, it cannot be concluded that these programs promote clinically relevant improvements in the balance and mobility of these individuals.

Another popular training type for this patient population is balance training because it is well known that individuals with MS are at an increased risk of falling due to lower levels of postural control. These training programs typically meet 2-4 times each week for 45-60 minutes over a 3-10 week period. The activities within balance training protocols are highly variable between studies and have focused on the specific balance deficits of individual subjects, the use of biofeedback or sensory integration, or employing more traditional balance exercises.[9,17,51,57,78,113] Improved postural balance occurred after these training programs and some also reported improvements in fatigue, depression, walking capacity, and a reduction in the number of falls reported by participants. While these programs have been found to be beneficial to promoting improvements in balance, it is relatively unknown whether there is an optimal type of activity for stimulating improvements in postural control.

Finally, recent investigations have also explored the use of novel therapeutic paradigms such as tai chi or exergaming with individuals who have MS.[12,53,68,87] These programs typically meet 1-3 times per week for 30-90 minutes and can extend for up to six months. Exergaming training using the Wii game console resulted in similar improvements as more traditional therapeutic paradigms in balance and walking; it also had greater adherence to the training program than more traditional programs.[87] Activities that challenged the balance of individuals with MS such as yoga, tai chi, and kickboxing promoted improvements in balance, coordination, walking ability, and fatigue.[12,53,68] Therefore, it appears that even non-traditional types of activities may be beneficial to the balance and mobility of individuals with MS.

The majority of these previous investigations suggest that exercise and physical therapy protocols are not detrimental to individuals with MS; rather, these types of programs may promote beneficial changes in the balance and mobility of these individuals. However, there is a lot of variability within these programs, not only in the types of activities being performed, as displayed above, but also in the amount of activity being done. These previous investigations were anywhere from three to 24 weeks in length with the majority of them being shorter than 12 weeks long. Usually these training programs had between two to four sessions per week and lasted anywhere from 30 to 90 minutes in length per session. Therefore, it is relatively unknown how much or what type of activity is needed to promote clinically relevant improvements in the balance and mobility of individuals with MS.

Purpose of Dissertation

A primary purpose of this dissertation is to gain a more complete understanding of the compensatory strategies employed by individuals with MS during walking. Specifically, this dissertation will interrogate the mechanical work generated by the lower extremity joints during walking and seek to quantify the motor control of the ankle musculature. It is hypothesized that the ankle joint of individuals with MS will generate a reduced amount of positive mechanical work during walking but that the hip joint will produce a substantially larger amount of positive mechanical work than normal. Moreover, it is hypothesized that individuals with MS will exhibit a lower amount of motor control at the ankle during a dynamic isometric contraction and that this lower amount of motor control will be related to the impairments in the mobility of these individuals. Potentially, the limitations in these areas contribute to the instability and mobility deficits of individuals with MS, thus leading these individuals to adopt compensatory strategies such as slower walking velocities and shorter step lengths. The outcomes from this main purpose will provide us with important information regarding the contributing factors to the limitations in balance and mobility of individuals with MS.

Another main purpose of this dissertation is to explore how to better target the balance and mobility limitations of individuals with MS through physical therapy interventions. Moreover, this dissertation will seek to provide new information regarding the optimal type and dosage of therapeutic interventions for promoting clinically relevant improvements in the gait and balance of individuals with MS. It is hypothesized that a high-frequency therapeutic intervention that utilizes motor adaptation techniques that focus on the ankle musculature will augment the results typically seen with more traditional therapeutic programs. Additionally, it is hypothesized that high-frequency therapeutic interventions will be able to promote improvements in the control of the ankle musculature and regularity of trunk accelerations during walking. The outcomes from this main purpose will challenge the traditional stance against high levels of activity for individuals with MS and provide valuable insight into the parameters important for improving the balance and mobility of individuals with MS.

The overall outcomes of this dissertation will provide a more complete understanding of the mobility of individuals with MS and the potential underlying causes of these mobility limitations. Additionally, it will provide foundational work on the type and dosage of physical therapy interventions that are beneficial to improving the posture and mobility of individuals with MS. Together, this knowledge will allow for the development of superior treatment options for individuals with MS, which potentially will target the underlying causes of the balance and mobility limitations for this patient population.

CHAPTER 1: INDIVIDUALS WITH MULTIPLE SCLEROSIS REDISTRIBUTE POSITIVE MECHANICAL WORK FROM THE ANKLE TO THE HIP DURING WALKING

Introduction

Multiple sclerosis (MS) is a progressive, autoimmune disease that causes inflammation and demyelination.[31] It is the most common disabling disease in young adults and currently affects about 570,000 individuals in the United States of America.[14,31] These individuals often face motor impairments which result from increased muscle weakness, latent muscular activity, spasticity and muscular fatigue.[13,40,90,116,126,134,147] Because of these motor deficits, individuals with MS often have balance limitations which make them highly susceptible to falling.[40] Potentially in order to compensate for this instability, individuals with MS often walk with shorter step lengths, slower walking velocities, slower cadences, and an increased amount of time spent in double support.[5,81,97]

Human walking has often been described using an inverted pendulum model.[18] In this model, the body's center of mass travels in an arch trajectory. At the end of the arch trajectory for one leg, the pendulum transfers to the other leg which proceeds in a similar manner. At this step-to-step transition point, the center of mass must be redirected, which requires mechanical work in order for the walking speed to remain constant.[43] Positive mechanical work occurs when mechanical energy is generated by the leg musculature, while negative mechanical work occurs when mechanical energy is dissipated or absorbed by the leg musculature. During the stance phase of gait, positive and negative mechanical work is distributed across the ankle, knee, and hip joints. During the stance phase, the ankle joint produces the majority of positive work, especially during late stance, and the knee joint typically produces negative work.[145] Both positive and negative mechanical work is generated by the hip joint but the positive work generally outweighs the negative work. Previous investigations have shown that the elderly and individuals with neurologic impairments (i.e., stroke) tend to redistribute the mechanical work across the joints in order to compensate for decreases in muscle strength, the inability to generate rapid torque, and limited range of motion about a joint.[39,71,99,108] A common redistribution pattern that occurs in order to compensate for the reduced positive work produced by the ankle joint is that the hip joint generates an increased amount of work.

It has been suggested that the neuromuscular impairments seen in the ankle plantarflexor musculature have devastating effects on the mobility of individuals with MS.[63,134,147] Specifically, ankle muscle weakness, spasticity, and altered muscle recruitment have been cited as major contributors to the slower walking speeds seen in this patient population.[134,147] Additionally, individuals with MS typically have limited range of motion and reduced power generation at the ankle.[63,81,97] The reduction in power generation at the ankle is thought to be a predictor of a reduced step length and walking velocity in individuals with MS.[63] It is possible that individuals with MS may adopt a hip compensatory strategy during gait due to the limited amount of mechanical work generated by the ankle joint. Although this conjecture seems plausible, we currently have limited insight on how MS impacts the mechanical work produced by the lower extremity joints. Further exploration of the mechanical work may provide new insights on compensatory strategies that individuals with MS tend to utilize to overcome impairments at the ankle.

The primary purpose of this investigation was to explore the net mechanical work at the ankle, knee, and hip joints of the less impaired and more impaired legs of individuals with MS. Secondarily, this investigation sought to interrogate the differences in distribution of work across joints between individuals with MS and a cohort of healthy age-matched adults. The main hypothesis was that the ankle joints of the individuals with MS would produce a reduced amount of positive mechanical work and that the positive mechanical work would be redistributed to the hip joint. Secondarily, we hypothesized that both limbs of the individuals with MS would generate less net mechanical work during the stance phase of gait than what would be seen in the healthy age-matched adults.

Methods

Fifteen individuals with either relapsing-remitting or secondary progressive MS participated in this study (Mean Age: 53.1 ± 7.6 years; 10 female; EDSS: 4.4 ± 0.3). Potential subjects with MS were not eligible for the study if they had a relapse within the last six months or a change in medication in the last three months. Additionally, subjects were excluded if they had another major co-morbidity such as uncontrolled pain or hypertension. Fifteen healthy, age and gender matched adults were enrolled and acted as a control group (Mean Age: 53.5 ± 7.4; 10 female). The control group subjects were free from any known orthopedic or neurological impairments. All experimental procedures were reviewed and approved by the University of Nebraska Medical Center Institutional Review Board. Additionally, all subjects provided written informed consent before participating in the experimental procedures. All subjects with MS were able to walk independently without an assistive device (i.e., cane, walker, ankle-foot orthosis) despite some subjects reliant upon an assistive device for community ambulation (See Table 1).

Subjects walked barefoot at a self-selected pace along a 16-meter walkway instrumented with four force platforms (1200 Hz; Advanced Mechanical Technology, Inc., Watertown, MA, USA). Reflective markers were placed bilaterally upon the lower extremities based on a modified Helen Hayes marker set, and these markers were tracked by an eight-camera three-dimensional motion capture system (120 Hz; Vicon Motion Systems Ltd., Centennial, CO, USA). All subjects completed at least three trials where there were consecutive foot contacts within the boundaries of separate force plates. Subjects were allowed to rest in between each walking trial so as to not become fatigued during the experimental procedures.

The walking trials were analyzed using custom Matlab programs (The Mathworks, Inc., Natick, MA, USA). Walking velocity (meters/second) was calculated based on the trajectory of a marker placed upon the pelvis. Step length (meters), step width (meters), and cadence (steps/minute) were calculated using the trajectories of the heel markers on each foot. The Vicon Plug-In Gait module was utilized to calculate the joint moments and joint angular velocities. Joint powers were calculated from the product of the respective joint moments and joint angular velocities. The positive and negative mechanical work at the ankle, knee, and hip joint were found by integrating the respective power curves during the stance phase. The net mechanical work at each joint was found by summing the positive and negative work together. All mechanical work was normalized to each subject’s body mass. For the subjects with MS, the mechanical work for both the more and less impaired legs were found for the stance phase of gait for each trial. For the control subjects, the mechanical work for the non-dominant leg was found for the stance phase of gait for each trial.

Statistical Analysis

Independent samples t tests were used to determine the differences in the spatiotemporal kinematics between the two groups. A 2 x 3 mixed model ANOVA (Leg x Joint) was used to interrogate the differences in the mechanical work at the ankle, knee and hip joints between the more and less impaired legs of the MS subjects. Additional separate 2 x 3 mixed model ANOVAs (Group x Joint) were used to interrogate the differences in the mechanical work at the ankle, knee and hip joints between either leg of the MS subjects and the non-dominant leg of the control subjects. An alpha level of 0.05 was used to interrogate all data for significance. The data is reported as the mean ± standard error of the mean.

Table 1: Subject Demographics for the MS Group

Subject	Age	Gender	MS Diagnosis	Years with MS	EDSS	Assistive Device for Community Ambulation
1	57	F	RR	19	4.0	Cane
2	48	M	SP	12	5.5	Cane
3	50	F	RR	12	3.5	None
4	57	F	RR	12	4.0	None
5	55	M	SP	4	4.5	None
6	53	M	RR	15	4.0	None
7	58	F	RR	33	6.0	Cane/Walker
8	36	F	SP	14	6.5	Walker
9	57	M	RR	16	4.0	None
10	72	F	RR	34	4.0	Cane
11	53	F	RR	20	5.0	Walker
12	50	F	RR	23	3.0	None
13	53	M	RR	14	3.0	None
14	48	F	RR	20	4.0	Cane
15	50	F	RR	15	4.5	Cane

Abbreviations. MS, multiple sclerosis; RR, relapsing-remitting multiple sclerosis; SP, secondary progressive multiple sclerosis

Results

All subjects in both groups completed all the experimental procedures. However, two subjects from the group with MS and one subject from the control group did not have evaluable data. Therefore, the final analyses were performed on 13 subjects with MS and 14 control subjects.

Spatiotemporal Kinematics

The subjects with MS walked slower than the control subjects (MS: 0.95 ± 0.02 m/s; Controls: 1.17 ± 0.02 m/s; $p < 0.001$). Additionally, the subjects with MS had shorter step lengths (MS: 0.51 ± 0.01 m; Controls: 0.58 ± 0.01 m; $p < 0.001$) and slower cadences (MS: 104.1 ± 3 steps/min; Controls: 117.6 ± 3 steps/min; $p = 0.001$). There was no difference in step widths between the two groups (MS: 0.18 ± 0.01 m; Controls: 0.17 ± 0.01 m; p = 0.60).

Mechanical Work

More Impaired Leg vs Less Impaired Leg

There was a significant Joint main effect (p = 0.04). Post hoc analyses indicated that the hip joint produced more positive mechanical work than the ankle joint (Hip: 0.080 ± 0.03 J/kg; Ankle: 0.005 ± 0.02 J/kg; p = 0.04) and knee joint (Knee: -0.017 ± 0.01 J/kg; p = 0.001). There was also a significant Leg main effect (p =0.02; Figure 2A), which indicated that there was a difference in the mechanical work produced by the respective legs. Evaluation of the data revealed that the less impaired leg produced positive mechanical work, while the more impaired leg produced negative mechanical work during stance. There was no significant Leg by Joint interaction (p = 0.15).

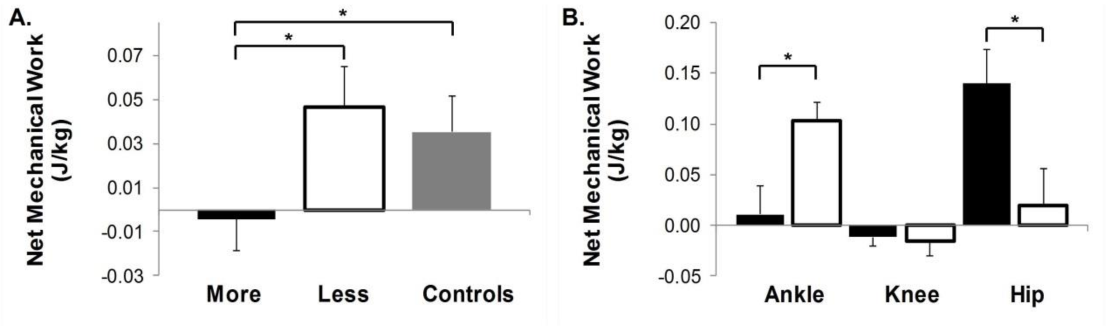

Figure 2: Mechanical Work Results. A) The Leg and Group main effects for the subjects with MS and the control group. This graph shows that the less impaired leg produced more positive mechanical work than the more impaired leg and that the control group produced more positive mechanical work than the more impaired leg. It also displays that the less impaired leg of the group with MS and the control group produce a similar amount of positive mechanical work. **B)** The Group by Joint interaction for the less impaired leg of the subjects with MS and the healthy control group. This graph shows that the ankle of the control subjects produced substantially more positive mechanical work than the ankle of the less impaired leg of the subjects with MS. It also shows that the subjects with MS produced a greater amount of positive mechanical work at the hip of their less impaired leg than the healthy control group. For this graph, the black bars represent the group with MS and the white bars represent the healthy control group. * indicates p ≤ 0.05.

Controls Leg vs MS Less Impaired Leg

There was a significant Joint main effect (p = 0.02). Post hoc analyses indicated that the ankle (0.058 ± 0.02; p = 0.002) and hip joints (0.078 ± 0.03; p = 0.002) produced more positive mechanical work than the knee joint (-0.014 ± 0.01), but there were no differences between the positive mechanical work generated at the ankle and hip joints (p = 0.65). There was no Group main effect (p = 0.79). However, there was a significant Group by Joint interaction (p = 0.01; Figure 2B). Upon further inspection, the control group produced more positive mechanical work at the ankle than the less impaired leg of the subjects with MS (p = 0.01), but the hip joint of the less impaired leg of the subjects with MS produced more positive mechanical work than what was seen in the control group (p = 0.02). There was no difference between the groups for the mechanical work produced at the knee (p = 0.81).

Controls Leg vs MS More Impaired Leg

There was a significant Joint main effect (p = 0.04). Post hoc analyses indicated that the knee joint produced significantly less positive mechanical work than the ankle joint (Knee: -0.024 ± 0.01; Ankle: 0.053 ± 0.02; p < 0.001) but not the hip joint (Hip: 0.020 ± 0.03; p =0.11). Additionally, there was no difference between the amount of positive mechanical work generated by the ankle and hip joints (p = 0.35). There was a significant Group main effect (p = 0.02; Figure 2A) which indicated that there was a difference between the mechanical work produced by the leg of the respective groups. Evaluation of the data displayed that the more impaired leg produced negative mechanical work while the controls produced positive mechanical work. There was no significant Group by Joint interaction (p = 0.21).

Discussion

The results from our study indicated that individuals with MS generate significantly less positive mechanical work with their more impaired leg than their less impaired leg and the non-dominant leg of a healthy control group. We also saw that the ankle joint of the less impaired leg produced less than half as much positive mechanical work as the ankle joint of the healthy control group. However, the hip joint of the less impaired leg of the subject with MS produced more than double the positive mechanical work produced at the hip of the healthy control group. These results suggest that individuals with MS may adopt a compensatory gait strategy that relies on the hip for generating the majority of the positive mechanical work needed for sustainment of gait speed.

It is well established that individuals with MS walk with shorter step lengths, slower velocities, and slower cadences than healthy age-matched adults.[5,81,97] Our results were no exception with our MS subjects walking with a 19.2% reduction in walking velocity, a 14.2% reduction in step length, and a 10.4% reduction in the cadence from the values of our age-matched, healthy control group. Moreover, our subjects had a slower average walking velocity, step length, and cadence than participants in previous investigations indicating that potentially our subjects had greater mobility impairments than the subjects in these prior investigations.[63,81,97] The ankle plantarflexor musculature is an important parameter for regulating speed and is vital for generating the majority of the positive mechanical work to sustain the walking speed.[108] Along these lines, previous investigations have speculated that the ankle joint might be a limiting factor for the mobility of individuals with MS.[63,134,147] The outcomes from the current study support this notion by showing that the ankle joint of the less impaired leg of individuals with MS produces a lower amount of positive mechanical work during the stance phase of gait than normal. The reduction in positive mechanical work at the ankle is potentially due to the presence of spasticity, significant muscle weakness, and/or altered muscle recruitment patterns often seen in individuals with MS.

The outcomes from the current study display that individuals with MS produce significantly less positive mechanical work with their more impaired leg than their less impaired leg and healthy age-matched adults. These results were not surprising because previous investigations have observed asymmetry between the legs of individuals with MS in muscle strength, power generation, and postural response latencies.[13,29,79,90] The asymmetry between legs may be due to increased muscle weakness or spasticity caused by asymmetrical damage to the brain and spinal cord, which could limit one's ability to produce an appropriate amount of mechanical work during walking. It is also possible that the somatosensory conduction is better in one leg, thus promoting better functioning of this leg over the other.[13] Potentially, a therapeutic intervention which targeted the more impaired leg of individuals with MS may promote more symmetry of mechanical work generation between the legs, thus promoting better mobility.

Our results display that individuals with MS redistribute their mechanical work such that the hip joint of their less impaired leg generates a greater amount of positive work than what is commonly seen in healthy age-matched adults. These results are similar to previous investigations that have found a hip dominant strategy is employed by the elderly or clinical populations, such as stroke patients, who have reduced functioning of their ankle plantarflexors.[39,71,99,108] It has previously been suggested that individuals with MS are unable to adapt their control strategies because a prior investigation did not observe an increase in power generation at the hip during the stance phase of gait despite having a decrease in power generation at the ankle.[63] Potentially, the discrepancy between this previous investigation and the current results may be contributed to the fact that we evaluated the mechanical work over the entire stance phase of gait while the previous investigation focused on discrete time points during stance. Nevertheless, our results do suggest that individuals with MS may have the ability to adapt their neuromuscular control to rely upon stronger or better functioning hip musculature to maintain their walking ability.

It is well known that individuals with MS tend to have a higher metabolic cost during walking than healthy individuals.[105,114] This higher metabolic cost has been suggested to be due to increases in muscle spasticity and a higher overall level of disability.[105,114] However, it is possible that the higher metabolic cost is related to the hip strategy adopted by individuals with MS to compensate for the decreased ability to generate mechanical work at the ankle. This notion is supported by a previous investigation that has shown that an increased reliance upon the hip for generation of positive mechanical energy results in a higher walk metabolic cost.[125] This increase in metabolic cost has been speculated to be due to a decreased reliance upon the metabolic free elastic energy provided by the Achilles tendon during gait. Potentially, therapeutic strategies that target the ankle musculature may be able to promote the adoption a more normal strategy for generating the majority of mechanical work at the ankle in individuals with MS, which in turn would result in better mobility and a lower cost of walking.

The differences in walking speeds between the two groups in our study could potentially have influenced the mechanical work produced at each joint. Joint torques and powers, especially at the ankle, have been found to be directly related to walking velocity.[19,84,92,153,154] Specifically, as cadence or velocity increases, joint powers and torques tend to increase as well. Thus, it is expected that there would be a lower amount of positive mechanical work generated when walking at slower velocities. Moreover, previous investigations that have manipulated gait speed with healthy young adults have produced similar alterations in torque and power production as those commonly seen in the gait of elderly adults, who typically walk at slow velocities.[153,154] Therefore, it is possible that the reduced positive mechanical work at the ankle of the less impaired leg of the subjects with MS is due to the slower walking velocities seen in these subjects when compared to the healthy control group. However, previous investigations where elderly and young adult subjects walked at similar speeds still identified that elderly individuals redistribute their joint torques and powers towards a hip dominant control pattern.[39] Thus, it is possible that the slower walking velocity of our group with MS did not significantly impact the distribution of mechanical work across the joints. Future investigations should challenge our results by controlling for walking velocity. This experimental approach may more accurately identify the mechanical work produced by the respective joints of individuals with MS during gait, and the potential redistribution to the hip that may occur as a compensatory mechanism to maintain gait speed in individuals with MS.

In conclusion, our results display that individuals with MS generate a lower amount of positive mechanical work at the ankle than healthy adults but they are still able to produce a similar amount of positive mechanical work with their less impaired leg as healthy adults. This is because individuals with MS appear to adopt a hip strategy with the less impaired leg in order to compensate for the decreased amount of positive work generated at the ankle. Future investigations should continue to explore this potential compensatory strategy so that we may have a more complete understanding of the mobility impairments of this clinical population and better target these impairments with therapeutic interventions.

CHAPTER 2: ERRORS IN THE ANKLE PLANTARFLEXOR FORCE PRODUCTION ARE RELATED TO THE GAIT DEFICITS OF INDIVIDUALS WITH MULTIPLE SCLEROSIS

Introduction

Multiple sclerosis (MS) is a demyelinating disease that affects about 570,000 individuals in the United States.[14] These individuals often face motor impairments that result from muscular weakness, latent muscular activity, spasticity, and muscular fatigue.[13,90,116,126,134,139,147] As a result of these motor deficits, individuals with MS often have balance limitations which make them highly susceptible to falling. It has been suggested that individuals with MS may compensate for their balance limitations by walking with shorter step lengths, slower walking velocities, slower cadences, and an increased amount of time spent in double support.[5,81,97] It has been speculated that the neuromuscular impairments in the ankle plantarflexor musculature, such as increased muscle weakness or poor motor control, have major effects on the mobility; however, this notion has not been well explored.[63,81,97,134,147]

Control of the ankle plantarflexor musculature can be quantified by the amount of variability or error that occurs in a submaximal isometric force matching task.[86] Previous investigations have used both continuous and dynamic isometric force matching tasks to explore the motor control of the lower extremities.[15,22,23,129] During a continuous isometric task, subjects attempt to generate and sustain a force that matches a static target force value, while for a dynamic isometric task subjects attempt to ramp up and down their isometric force production to match a target force that often has a parabolic shape. While it is normal for a force trajectory to display a small amount of variability or error in its pattern, an increased amount of error is thought to reflect an inaccurate control of the muscular force production. Additionally, it is common for a more dynamic isometric motor task to display a higher amount of variability or error than a continuous isometric contraction. This has been speculated to be due to the higher rate of force production or that the motor command must be constantly altered during a dynamic motor task.[22]

Prior investigations have shown that a greater amount of variability in a submaximal continuous isometric contraction performed with the ankle plantarflexors is related to decreases in standing postural stability.[86,100] Additionally, in our previous investigation, we displayed that a heightened amount of variability in the continuous isometric ankle plantarflexor force production was related with the degree of upright postural balance impairments seen in individuals with MS.[36] Furthermore, a reduction in the amount of variability in the isometric plantarflexion force production seen after individuals with MS undergo physical therapy was related to the degree of improvements seen in their standing postural control. However, the reduction in the variability of the continuous isometric plantarflexion force production was not related to the improvements in walking ability. Other prior investigations have also struggled to find a relationship between the variability within a continuous isometric contraction and functional abilities such as walking or climbing stairs.[15,95,129] Potentially, this is due to the dynamic nature of the ankle motor control during these functional tasks. Therefore, the use of a submaximal, dynamic isometric force matching task may be more useful in identifying the motor control deficits of the ankle musculature that may limit walking ability.

The primary purpose of this study was to evaluate the variability of the ankle plantarflexor musculature of individuals with MS while completing a dynamic isometric target matching task. Secondarily, we sought to determine whether the amount of variability or errors in the dynamic ankle plantarflexion force production is related to the alterations in the gait patterns that typically occur with MS. Our overarching hypothesis was that individuals with MS would have more errors in their dynamic ankle isometric force production, and that these errors would be directly related to the mobility impairments of individuals with MS.

Methods

Fifteen individuals with either relapsing-remitting or secondary progressive MS (Mean Age: 53.1 ± 7.6 years; 10 female; see Table 2 for subject characteristics) and 15 healthy, age and gender matched adults (Mean Age: 53.5 ± 7.4 years; 10 female) participated in this research study. All experimental procedures were reviewed and approved by the University of Nebraska Medical Center Institutional Review Board. Additionally, all subjects provided written informed consent before participating in the experimental procedures. All experimental procedures were performed barefoot by the subjects without the use of any assistive devices (i.e., canes, ankle-foot orthoses, wheeled walkers).

Table 2: Subject Demographics for the MS Group

Subject	Age	Gender	MS Diagnosis	Years with MS	Assistive Device for Community Ambulation
1	57	F	RR	19	Cane
2	48	M	SP	12	Cane
3	50	F	RR	12	None
4	57	F	RR	12	None
5	55	M	SP	4	None
6	53	M	RR	15	None
7	58	F	RR	33	Cane/Walker
8	36	F	SP	14	Walker
9	57	M	RR	16	None
10	72	F	RR	34	Cane
11	53	F	RR	20	Walker
12	50	F	RR	23	None
13	53	M	RR	14	None
14	48	F	RR	20	Cane
15	50	F	RR	15	Cane

Abbreviations. MS, multiple sclerosis; RR, relapsing-remitting multiple sclerosis; SP, secondary progressive multiple sclerosis

Motion Analysis of Gait

An eight camera three-dimensional motion capture system (120 Hz; Vicon, Centennial, CO, USA) was used to track a modified Helen Hayes reflective marker set that was placed bilaterally on the lower extremities of each subject. A standing calibration with a knee-alignment device was captured at the beginning of the data collection for each subject in order to ensure that the markers were correctly positioned. Subjects were instructed to walk at their self-selected preferred pace along a pathway instrumented with four force plates (Advanced Mechanical Technology, Inc., Watertown, MA, USA). All subjects completed a sufficient number of walking trials in order to acquire at least three trials with consecutive foot contacts where each foot was positioned completely within the boundaries of separate force plates. Walking trials were completed at each subject's own pace and sufficient rest was provided as needed. The Vicon Plug-In Gait module was utilized to calculate the moments generated by the ankle musculature during walking. These moments were normalized to the body weight for each subject.

The variables of interest from the gait data included the maximum moment generated by the ankle at toe-off of the most affected limb for the subjects with MS or the non-dominant limb for the control group. Additionally, the spatiotemporal kinematics of gait including step width (meters), step length (meters), walking velocity (meters/second), and cadence (steps/minute) were calculated from the motion capture data. The data from the respective trials were averaged for the final analyses.

Dynamic Isometric Ankle Force Control

Dynamic isometric control of the ankle plantarflexors was interrogated using a plantarflexion task where the subjects were required to exert the appropriate amount of isometric force to accurately match a target force that had a sine wave pattern. The MS subjects used their most affected limb and the control subjects used their non-dominant limb for the target matching task. Participants sat on the chair of an isokinetic dynamometer (Biodex, Inc., Shirley, NY) with the backrest angle at 90°. The knee of the subject was fully extended and the ankle was in a neutral position with the subject's foot strapped onto a metal foot place. Two maximal isometric voluntary contractions were completed, and the highest maximal voluntary torque (MVT) was used to calculate a 20% MVT target force value. The MVT was normalized to each subject's body weight and included in the final analyses.

The sine wave was generated using a custom LabView (National Instruments Inc., Austin, TX, USA) program which employed the use of the Simulate Signal Express VI. The amplitude of the sine wave that each subject was required to follow was set at the 20% MVT value calculated for each subject and the frequency of the sine wave was 0.5 Hz. The timing parameters in the VI were set such that there were 1000 samples per second and either three or seven samples were used to create the sine wave output signal. The trials with three samples displayed the sine wave within 35 seconds and will be referred to as the Slow Trials. The trials with seven samples displayed the sine wave within 15 seconds and will be referred to as the Fast Trials. Constant visual feedback for all trials was provided to the subjects via a computer screen ~1 m in front of them. The program displayed the target as a hollow, green box which moved up and down according to the pattern of the generated sine wave. Additionally, the program provided subjects with feedback about the actual force being produced in real time, which was represented by a solid, red circle (Figure 3). Subjects were instructed to follow the target in such a way to place the red circle inside the hollow white target box as best as they could throughout the entire sine wave motion. All subjects completed three trials of the target matching task for both the Slow Trials and the Fast Trials, for a total of six trials. The order of the trials was randomized between subjects.

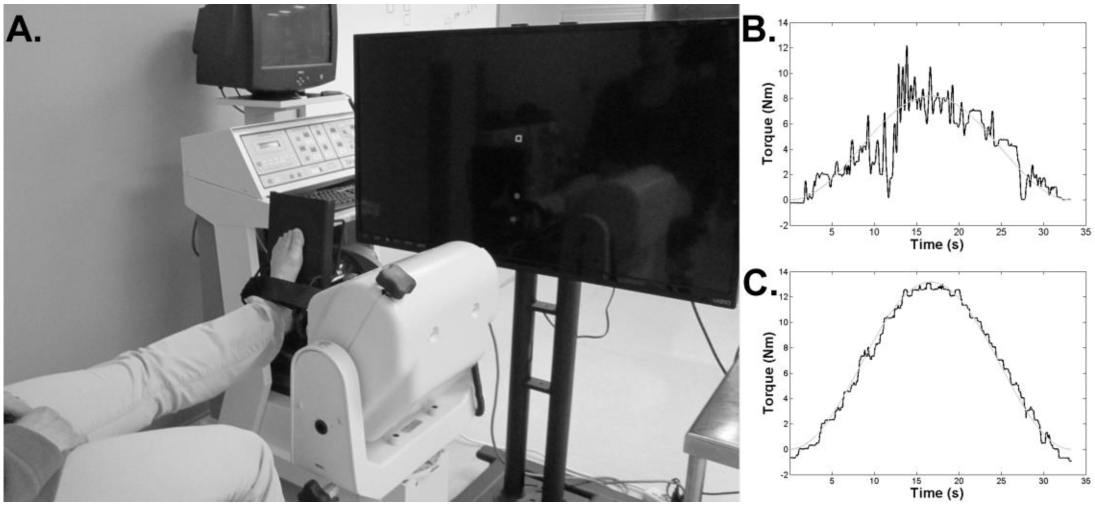

Figure 3: Experimental Set-up and Exemplary Torque Graphs. A) The experimental set-up for the dynamic isometric ankle force matching task. **B)** A representative force trajectory graph for an individual with MS during a Slow Trial. **C)** A representative force trajectory graph for a healthy, control subject during a Slow Trial. Inspection of panels B and C clearly show that the individual with MS had a greater amount of error in their dynamic ankle isometric force production than the healthy control.

The torque output was filtered using a fourth order Butterworth filter with a 25 Hz cutoff. All target-matching data was normalized to each subject's 20% MVT in order to allow for comparison across subjects. The data from the three separate trials for each trial type (Slow Trial or Fast Trial) was averaged together for the final analyses. The root mean square (RMS) was calculated on each trial using the following equation:

$$\text{Equation 1:RMS}=\sqrt{\frac{1}{\mathrm{N}-1}\sum_{\mathrm{i}=1}^{\mathrm{N}}(\mathrm{x_i}-\mathrm{t_i})^2}$$

where N is the number of data points in the time series, $\mathrm{t_i}$ is the target force, and $\mathrm{x_i}$ is the torque sample. The RMS allows for the interrogation of the amount of error in the torque generation of each trial.

Statistical Analyses

All statistical analyses were performed using IBM SPSS Statistics 22 statistical software (IBM Corp., Armonk, NY, USA). A mixed two-way repeated measures ANOVA

(Group × Trial Type) was used to compare the differences in the RMS between the groups (MS Group vs Control Group) and trial types (Slow Trials vs Fast Trials). Independent samples t tests were used to interrogate the differences between the two groups for the spatiotemporal kinematics, the maximal ankle moment generated at toe-off during gait, and the normalized MVT. Additionally, Spearman rho rank order correlations were calculated between the RMS, MVT, and all gait variables to determine if the amount of error in the dynamic isometric torque control of the ankle plantarflexors was related to the gait characteristics and muscle strength. An alpha level of 0.05 was used to interrogate all data for significance. The data is reported as the mean ± standard error of the mean.

Results

All 30 subjects completed each portion of the data collection. However, one subject from each group was excluded from the final analyses due to not having evaluable data for all measures.

Gait Variables

The group with MS displayed shorter step lengths (p=0.001; Figure 4A), slower cadences (p=0.006; Figure 4B), and slower walking velocities (p<0.001; Figure 4C) than the healthy adult group. There were no differences in the step widths between groups (MS: 0.18 ± 0.01; Controls: 0.17 ± 0.01; p>0.05). Additionally, subjects with MS had a lower maximal ankle joint moment at toe-off (p=0.017; Figure 4D) than the healthy adults during gait.

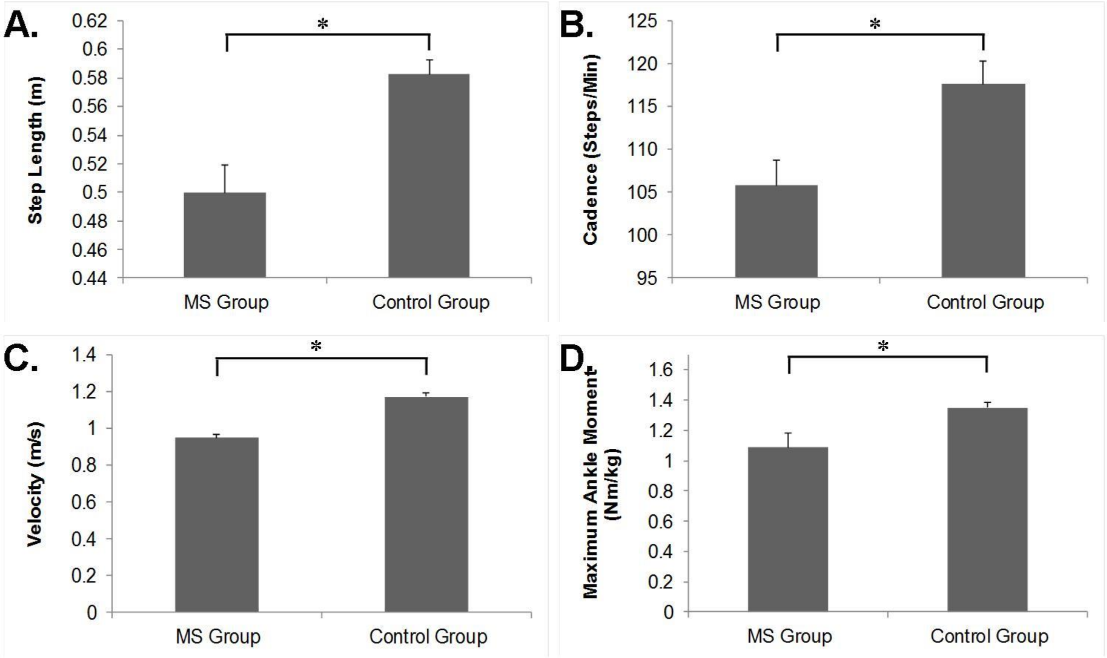

Figure 4: Spatiotemporal Kinematics and Maximal Ankle Moment Results. The between group differences for **A)** step length, **B)** cadence, **C)** walking velocity, and maximum ankle moment at toe-off during walking. These results show that the individuals with MS walked slower and had a reduced step length, slower cadence and generated a lower moment by the ankle at toe-off. * indicates $p<0.05$.

Dynamic Isometric Ankle Force Control

The group with MS had a significantly lower normalized MVT than the healthy adult group ($p=0.007$; Figure 5A). This indicates that our subjects with MS were significantly weaker than the healthy adults, as one would expect. There was a significant Trial Type main effect ($p<0.001$; Figure 5B) for the RMS, with the Fast Trials having a higher RMS than the Slow Trials. Hence, indicating that more errors occurred when the isometric force was generated at a faster rate by the ankle. Additionally, there was a significant Group main effect ($p=0.021$; Figure 5C) for the RMS with the subjects with MS having a higher RMS than the control group. This main effect displayed that there were more errors overall in the isometric ankle force control of the individuals with MS than in the healthy adults. There was no significant Group by Trial Type interaction ($p>0.05$).

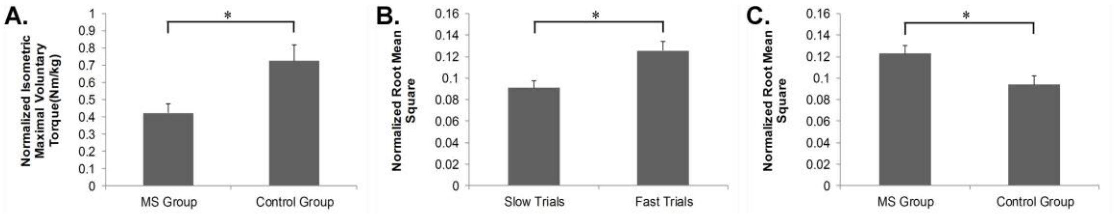

Figure 5: Maximal Isometric Voluntary Torque and Root Mean Square Results. A) The between group differences for the normalized maximal voluntary torque. This graph shows that the group with MS had weaker ankle plantarflexors than the healthy controls. **B)** The Trial Type main effect for the normalized RMS of the torque during the dynamic isometric force matching task. This graph shows that there were more errors generated by both groups during the Fast Trials compared with the Slow. **C)** The Group main effect for the normalized RMS of the torque during the dynamic isometric force matching task. This graph shows that the group with MS overall had greater errors in the dynamic isometric ankle force production for both the Slow and Fast Trials compared with the healthy controls. * indicates $p<0.05$.

Root Mean Square Correlations

All correlations between the RMS of the Slow and Fast Trials, the gait variables, and normalized isometric MVT are reported in Table 3. The RMS of the Fast Trials was negatively correlated to the maximal ankle joint moment at toe-off during walking ($p = 0.012$), which indicated that greater errors during the Fast Trials are associated with lower maximal moments generated by the ankle. Both the RMS of the Slow and Fast Trials were negatively correlated to the step length during walking (RMS Slow: $p = 0.002$; RMS Fast: $p = 0.011$). This indicated that greater errors during either trial type were associated with shorter step lengths. Additionally, the RMS of the Slow Trials was negatively correlated with walking velocity ($p = 0.004$), which indicated that a greater amount of error in the Slow Trials was associated with slower walking speeds.

Maximal Voluntary Torque Correlations

There was a positive correlation between the normalized MVT and the maximal ankle moment at toe-off during walking ($r = 0.579$, $p=0.001$). This correlation indicated that individuals that generated a weaker torque also tended to have lower moments generated by the ankle during walking. The RMS of both the Slow and Fast Trials were negatively correlated with the normalized MVT (RMS Slow Trials: p=0.005; RMS Fast Trials: p<0.001). These correlations indicated that individuals that had a weaker maximal torque also tended to have greater errors in the dynamic ankle isometric target matching tasks.

Table 3: Spearman rho rank order correlations between the RMS, the gait variables, and normalized MVT.

	Walking Velocity	**Step Length**	**Step Width**	**Cadence**	**Maximal Ankle Moment**	**Normalized Isometric MVT**
RMS Slow	-0.523*	-0.553*	-0.028	-0.262	-0.235	-0.518*
RMS Fast	-0.320	-0.471*	-0.106	0.026	-0.469*	-0.624*

* indicates p < 0.05.

Discussion

Our study sought to quantify the motor control of the ankle plantarflexor musculature of individuals with MS during a dynamic isometric force matching task. Additionally, our study explored the relationship between the motor control deficits in the ankle plantarflexor force production and the walking alterations that occur with MS. The outcomes from our study indicated that individuals with MS had greater errors in the dynamic isometric ankle force production. Not surprisingly, our subjects with MS also walked with altered spatiotemporal kinematics, and had a reduced maximal ankle moment at toe-off during walking than the healthy control group. In addition, the subjects with MS also had weaker ankle plantarflexors than the healthy adult group as demonstrated by the lower normalized isometric MVT generated by the subjects with MS. The increase in error during the dynamic isometric ankle force matching task was related to the decreases in step length and walking speed, decreases in maximal moments at the ankle during the toe-off phase of walking, and the reduced strength of the ankle plantarflexor musculature. Altogether, these outcomes suggest that the walking limitations of individuals with MS may be partly due to errors in the control of the ankle plantarflexors during dynamic motor tasks such as walking.

There was a greater amount of variability or errors in the ankle isometric force production when completing the Fast Trials than the Slow Trials. This outcome was not surprising because previous investigations have found higher amounts of variability when the parameters of the motor task are altered to increase the speed and/or complexity of the task.[22,33,150] Systematic changes in variability also occur with an increased rate of force production or a higher movement velocity; this increase in variability may be due to altered motor unit recruitment or more variable motor unit discharge rates.[110] Potentially, the differences seen in this investigation may be related to the rate of the change in the isometric force production between slow and fast conditions. Alternatively, we suggest that the differences may be related to the ability to utilize feedback during the motor task to make proper adjustments to minimize the amount of error in the motor performance. During a slower motor task, one is able to utilize the proprioceptive and visual feedback while there may not be sufficient time to process this information during a faster motor task.

The individuals with MS in our study displayed more errors in their ankle plantarflexion force generation than our healthy adult group. This result implies that the control of the precision of the dynamic force production of the ankle plantarflexors in individuals with MS is likely aberrant. Previous electroencephalography investigations have suggested that the damage upon the central nervous system caused by MS may impact the cortical activations associated with the production of motor actions.[93,94] Additionally, transcranial magnetic stimulation studies have shown slowed transmission of the motor command along the corticospinal tract, which would result in altered movement patterns.[50,73] Moreover, individuals with MS have slowed somatosensory conduction which may also influence the rate at which information can be received and processed for proper execution of the motor task.[13] Altogether these prior results suggest that the increased amount of error in the dynamic isometric force production of our subjects with MS may reflect the damage within the corticospinal tracts and/or the sensorimotor cortices.

The individuals with MS had significantly weaker plantarflexors than the age-matched controls, which is aligned with what has been reported in prior studies.[3,82,90,116,120,139] However, our results are novel because they show that the subjects with weaker muscles also tended to have more errors in their dynamic ankle force production. Previous investigations have found that weaker individuals of any age have higher amounts of variability in the force generation patterns of their upper extremities.[135] It has also been previously shown that weaker muscles typically have a more variable motor output due to the higher motor unit firing rates and fewer active motor units.[55] Potentially, the heightened errors seen in the dynamic force production of the individuals with MS may be related to the decreased and more variable motor unit discharge rates as well as incomplete motor unit recruitment.[44,82,120] Previous investigations suggest that resistance training programs can decrease the motor unit firing rate variability and influence the motor unit synchronization, thus resulting in better motor control.[85,127] Possibly, a progressive resistance training program may improve the motor control of the ankle muscular force production.

The subjects from our study walked with slower and more reduced spatio-temporal kinematics than what has been previously reported for individuals with MS suggesting that our subjects potentially had more disability than those in previous investigations.[63,81,97] Additionally, this notion is supported by the lower peak ankle moment of the MS subjects in our study than those found in previous investigations.[63] Previous investigations have suggested that the reduced peak ankle moment is a predictor of reduced step lengths and walking speeds in individuals with MS.[63] The neuromuscular alterations of the ankle musculature of individuals with MS such as spasticity, decreased muscle strength, and impaired proprioception have been proposed as contributing factors to these gait limitations.[135,147] In our study, the reduced peak ankle moment generation during walking was related to weaker MVT. These results suggest that the decreased muscle strength in individuals with MS may be a contributing factor to the reduced maximal ankle torque generated during walking and indirectly the decreased spatiotemporal kinematics.

The increased amount of error in the dynamic ankle isometric motor task was also associated with the reductions in the spatiotemporal gait kinematics. Specifically, the error was related to the reduced step length and slower walking velocity. In addition to reduced spatiotemporal kinematics, the amount of error in the dynamic isometric ankle motor task was also related to reduced maximal moments generated by the ankle during gait. These results suggest that the deficits in the gait patterns of individuals with MS may not be solely due to the neuromuscular alterations such as muscle weakness. Rather, these outcomes suggest that the errors in the control of the ankle during gait may contribute to a higher amount of internal perturbations in the gait patterns in individuals with MS. This could potentially be why individuals with MS have higher amounts of variability in their spatiotemporal kinematics of gait.[32,132]

Previous investigations quantifying the relationship between continuous isometric contractions of the lower extremities and functional tasks in healthy populations have been inconclusive.[15,95,129] While Seynnes et al.[129] discovered a relationship between brief, stressful functional tasks, such as chair rising or stair climbing, and steadiness during a continuous isometric contraction with the knee, Manini et al.[95] failed to find such a relationship. Additionally, results from our recent therapeutic investigation suggested that improvements in continuous isometric motor control of the ankle musculature were not related to improvements in gait parameters in individuals with MS.[36] Our current results suggest that these inconclusive results may be due to the use of a continuous motor task rather than a dynamic motor task to quantify the motor control of the ankle plantarflexors. Future investigations should explore whether improved dynamic motor control of the ankle joint is related to improvements in the mobility of individuals with MS following therapeutic interventions.

CHAPTER 3: NEUROREHABILITATION STRATEGIES FOCUSING ON ANKLE CONTROL IMPROVE MOBILITY AND POSTURE IN PERSONS WITH MULTIPLE SCLEROSIS[a]

Introduction

Multiple sclerosis (MS) is a demyelinating disease that is typically diagnosed in adults who are between of 20-40 years of age and affects about 570,000 individuals in the United States.[14,52] These individuals are often faced with movement impairments that can result from muscular weakness, latent muscular activity, spasticity, and muscular fatigue.[13,20,90,116,120,126,134,139,140,147] In turn, these impairments are associated with balance deficits that make them highly susceptible to falls.[40] The neuromuscular impairments seen in the ankle plantarflexors have been specifically highlighted as having devastating effects on the mobility and standing postural balance of individuals with MS.[13,63,134,147] Despite this recognition, limited efforts have been made to find effective treatment strategies that will improve the performance of the ankle plantarflexor musculature of individuals with MS.[62]

Traditionally, individuals with MS were discouraged from participating in exercise-based or intense therapies because it was thought that these types of therapies would exacerbate the MS symptoms.[141] Therefore, traditional therapies emphasized compensatory techniques that conserved the individual's energy.[122,144] However, this notion has been challenged by prior investigations that have shown that aerobic exercise can result in moderate improvements in the walking speed and endurance of individuals with MS while having no deleterious effects upon their symptoms.[7,111] Rehabilitation

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[a] The material presented in this Chapter was previously published: Davies, B. L., Arpin, D. J., Volkman, K. G., Corr, B., Reelfs, H., Harbourne, R. T., … Kurz, M. J. (2015). Neurorehabilitation strategies focusing on ankle control improve mobility and posture in persons with multiple sclerosis. *Journal of Neurologic Physical Therapy, 39*, 1-8.

protocols targeting the postural control of individuals with MS have also produced improvements in balance and walking capacity and have reduced the fatigue status of these individuals as well.[17,57] Moreover, resistance training programs targeting the lower extremities of individuals with MS have displayed significant improvements in the strength of the knee flexors and ankle plantarflexors as well as improved gait kinematics and functional capacity of these individuals.[54,151] Clinically relevant improvements in the mobility of individuals with MS have also occurred following group fitness classes or combined strength and aerobic training programs.[68,104] Although the outcomes of these previous studies are promising, the expected outcomes across these studies are somewhat blurred with some individuals demonstrating large improvements, while other individuals are classified as non-responders. We suspect that the degree of the improvement may be related to the amount of change that occurs in control of ankle musculature, since it has been cited as a primary factor that limits the mobility and posture of individuals with MS.[13,40,147]

Control of the ankle plantarflexor musculature can be quantified by the amount of variability or error that occurs in a submaximal isometric force matching task.[86] It is normal for a steady-state force to fluctuate slightly around an average force value; however, an increase in this variability reflects an inaccurate control of the muscular force production.[21,22,25,27,46,86] Prior research has shown that a greater amount of variability in the submaximal steady-state ankle plantarflexor force production is related to a greater amount of postural sway.[86] This relationship suggests that improvements in the control of the ankle plantarflexors may result in improved postural balance. Despite these novel insights, the motor control of the ankle plantarflexor musculature of individuals with MS has not been well explored. Previous research has explored the strength and muscle physiology of the lower extremities of individuals with MS rather than the motor control of the lower extremity musculature.[20,90,116,139,151] Furthermore, it is relatively unknown if the current rehabilitation strategies for individuals with MS can improve the motor control of the ankle plantarflexor musculature.

The primary purpose of this study was to determine whether an intensive gait and postural balance neurorehabilitation protocol can improve the muscular control of the ankle plantarflexor muscles of individuals with MS. It was hypothesized that the muscular control of the ankle plantarflexor muscles would be improved after the rehabilitation protocol, and that this improved control would be reflected through a lower coefficient of variation (CV) during a submaximal steady-state contraction. The secondary purposes of this study were 1) to determine whether the neurorehabilitation protocol would also improve the postural control, ankle plantarflexion strength, and spatio-temporal gait kinematics, and 2) to determine the potential relationship between the amount of change in the ankle plantarflexion control and the amount of change in the postural sway and mobility after completion of the neurorehabilitation protocol.

Methods

Participants

Fifteen adults with relapsing-remitting or secondary progressive MS participated in this investigation (6 Male; Mean Age: 52.6 ± 9 years). The participants had an average Kurtzke Extended Disability Status Score of 5.4 ± 0.9, which indicated that on average the participants could walk independently for at least 100 meters. Descriptive characteristics of the 15 MS participants can be found in Table 4. Twenty healthy adults acted as a control group (4 Male; Mean Age: 45.1 ± 14.1 years). The MS group completed testing for all variables before and after completing the rehabilitation protocol, and the control group completed one testing session for all variables. All participants gave written informed consent as required as part of the approval by the Institutional Review Board of the University of Nebraska Medical Center (UNMC).

Table 4. Demographic and Clinical Characteristics of the Participants

Subject	Gender	Age (Years)	MS Type	MS Duration	Assistive Device	EDSS
1	Female	44	RR	17	None	4
2	Female	43	RR	11	Cane	6
3	Female	55	RR	30	None	4
4	Male	68	SP	9	Cane/AFO	6
5	Male	49	RR	12	AFO	5.5
6	Male	54	SP	18	None	5.5
7	Female	43	RR	12	Cane	6
8	Female	47	RR	17	Forearm Crutches	6.5
9	Male	61	RR	15	Cane/AFO	5.5
10	Male	53	RR	16	None	4
11	Female	66	RR	10	Cane	6
12	Female	45	RR	8	None	4
13	Male	59	SP	13	Cane/AFO	6
14	Female	42	RR	27	Walker/AFO	6.5
15	Female	60	SP	18	Cane	5.5

Abbreviations. EDSS, Expanded Disability Scale Score MS, multiple sclerosis; RR, relapsing-remitting multiple sclerosis; SP, secondary progressive multiple sclerosis; AFO, ankle foot orthosis.

Ankle Plantarflexion Control Measures

Isometric muscular control of the ankle plantarflexors was measured using an isokinetic dynamometer (Biodex, Inc., Shirley, NY). The participants sat on the chair of the dynamometer with the backrest angle at 90° with their knee fully extended and their ankle in a neutral position with their foot strapped onto a metal foot plate. Two maximal isometric voluntary contractions were completed, and the highest maximal voluntary torque (MVT) was used to calculate a target force of 20% MVT. Additionally, the highest MVT was used to assess muscular strength of the ankle plantarflexors. For the sub-maximal contractions, participants were instructed to generate a plantarflexion force that would match the 20% target on the screen and to hold it there as steadily as possible for 30 seconds. Constant visual feedback was provided to the participants using a custom LabView (National Instruments Inc., USA) program which displayed the target and actual force produced in real-time on a computer screen ~1 m in front of the them. Each participant completed two steady-state trials. The middle 15 seconds of each trial was evaluated in order to ensure that a steady-state contraction had been reached. The coefficient of variation (CV = [standard deviation of torque / mean torque]*100) for each trial was calculated, and the two trials were averaged together for each subject.

Postural Control Measures

Postural control was measured using the composite score from the Sensory Organization Test (SOT) (NeuroCom® International, Clackamas OR).[49,156] The SOT test consists of six different conditions that measure the integration of visual, somatosensory, and vestibular feedback for reducing the amount of postural sway. The amount of postural sway that occurred in each condition was measured through a force plate that was integrated within the system, and a composite score calculated by the NeuroCom software was used to assess the subject's overall postural sway. A higher composite score indicated a lower amount of postural sway.

Mobility Measures

The mobility of the participants was measured by having them walk across a digital mat that measured the gait spatiotemporal kinematics (GAITRite®, CIR Systems Inc., Sparta, NJ). Participants completed two trials at a preferred walking pace and two trials walking as fast-as-possible. The subjects in the MS group were allowed to use the assistive devices that they use on a daily basis (see Table 4). The two trials for each walking speed were averaged together for statistical analysis. The walking velocity (meters/second), step width (meters), step length (meters), and cadence (steps/minute) were calculated for both walking speeds.

Physical Therapy Intervention

The total intervention time period was 14 weeks long and was performed twice a day for five days each week. The initial two weeks of the program were completed on the UNMC campus under close supervision of a licensed physical therapist (BC, HR, or KV). The therapists used a standardized training protocol and an exercise log to organize and record the one-on-one training sessions. The initial two weeks of training were followed by 12 weeks of a home based program. The participant's progress during the at-home period was monitored by the physical therapist through weekly phone contact. Moreover, during the 12-week home-based program, each subject was required to keep an exercise log book that was used to record the exercises that were performed each session, level of perceived exertion, and how long each exercise was performed. All subjects also met with the researchers and the physical therapist every four weeks in person to evaluate how the home program was going and make adjustments as needed.

During the 2-week twice daily intervention, each 60-80 minute training session consisted of how to perform the prescribed warm-up, balance, and walking exercises; and how to safely progress and log their home based sessions. The standardized warm-up consisted of several repetitions of trunk and limb movements, as well as individual-specific stretches and coordination activities for the limbs. After the warm up, the therapist prescribed a 20-minute balance training program based on an initial assessment. Following the balance training, the participants completed 20 minutes of challenging treadmill and overground walking training based on each subject's assessed ability and need for an assistive device.

The balance training program consisted of challenging sitting/standing balance task such as sitting on an exercise ball or standing in a corner with the feet either on the floor or on a piece of foam with eyes closed. The objective of this training was to challenge and progress the participant’s balance incrementally within the session to maintain upright control despite altered visual and somatosensory inputs. For example, the participant might begin in a less challenging position for the first 5 minutes on foam with their feet ten inches apart, progressing to more challenging positions during subsequent 5-minute periods, returning to a less challenging position for the final 5 minutes. During this training, the therapist provided verbal and tactile cues for upright posture and relaxation of tense body parts, verbal cues to increase sensory awareness (i.e. location of pressure on the soles of feet), and observed the participant for the ability to meet the task’s demand (i.e. the number of touches to the wall). Based on these observations and standardized guidelines, the therapist would increase the demands of the postural training. Generally, no rest periods occurred during the balance sessions. A fan cooled participants during all training activities to minimize heat sensitivity. Additionally, during all balance exercises the participants were supplied with a table or chair in front of them so that they could reach out for temporary support as needed, and each participant wore a gait belt so that the therapist was able to provide balance assistance as needed.

The walking training included tasks such as forward, backward, or sideways walking on the treadmill with a harness used as needed for safety. The use of handrails, ramp, and speed were varied throughout the training to provide an appropriate level of intensity for each subject. Additionally, the therapist provided overground training indoors while varying walking direction, speed, using a less-supportive assistive device, and/or increasing dynamic balance activities. The therapist provided verbal and manual cues to assist participants to achieve a more normal gait pattern and visual feedback was provided to all participants by training in front of a mirror. A similar protocol as described above for the balance task was employed to progress each 5-minute training period. Participants were provided with short sitting rest periods as needed. The intensity of the activities was increased as tolerated and recorded. Generally, the increase in intensity was based on each subject's level of performance and fatigue of the previous session.

During the 12 weeks of at-home training, the participants continued to complete both the gait and balance training twice a day, five days each week. All exercises for both types of training were the same as they had learned in the initial two weeks of the training. On the final day of the initial two weeks of training, the physical therapist provided each subject with a home exercise log book, which overviewed the exercises that were to be performed and exemplary exercise sessions for each subject. All subjects were instructed to increase the demands of the training during the 12 weeks of home based training. A majority of the participants had a treadmill inside their homes and completed the entire home exercise program at his/her house. The participants who did not have a treadmill visited a fitness center in order to complete his/her treadmill walking. Additionally, since the training focused on over-ground activities, participants were encouraged to complete over-ground walks outside through his/her neighborhood. All participants were provided with pieces of foam in order to complete the static balance portion of each session. In order to ensure safety during the static balance exercises at home, participants were encouraged to complete the balance training activities standing next to a wall, chair or bed so that they were equipped with adequate support against falls.

Statistical Analysis

Paired t tests were used to determine if there was significant change between the baseline and 14-week data for the respective variables. Additional t tests were used to determine if there was a difference between the respective groups. The False Discovery Rate algorithm was used to adjust the alpha level in order to control the potential family-wise error rate that may occur when conducting multiple t tests.[6] Pearson correlation coefficients were calculated between the CV of the isometric contractions and respective variables for the MS group to determine if the change in the control of the ankle plantarflexors was related to a change in the respective mobility and/or postural sway outcome measures. Cohen's *d* was calculated to determine the effect sizes of the respective changes in all variables. The following guidelines were used to interpret the effect sizes: 0.2 is a small effect size, 0.5 is a moderate effect size, and 0.8 is a large effect size.[30] Results are displayed as means ± standard error of means and a p-value equal to or less than the corrected 0.03 alpha level were considered significant for all statistics.

Results

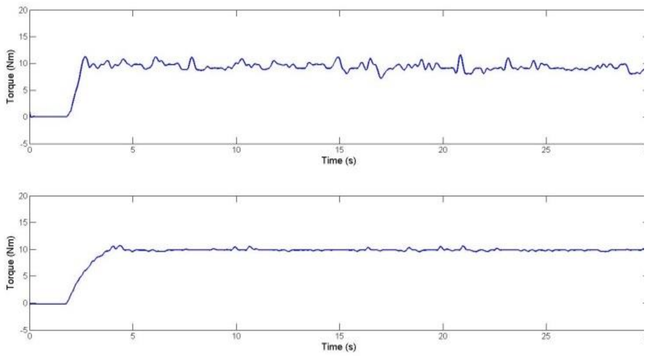

Figure 6: Exemplary Ankle Joint Torque Graphs. Exemplary graphs of ankle joint torques for an MS Subject before treatment (Top panel) and after treatment (Bottom panel).

All participants completed the 14-week neurorehabilitation protocol. Figure 6 represents the exemplary changes seen in the ankle plantarflexion force control that occurred after the rehabilitation. Inspection of the figure reveals that the participant had a sizeable amount of variability in the plantarflexion control before undergoing the rehabilitation training. However, this variability was considerably reduced after the participant completed the therapy. These graphical observations were supported by the group statistical analysis. Before the neurorehabilitation, the CV of the ankle plantarflexor steady-state torque for the individuals with MS was greater than the controls (p=0.03). After the rehabilitation protocol, there was a 45% reduction in the CV for the MS group (p=0.006). In addition, the amount of variability in the ankle plantarflexor torque of the MS group was no longer different from the control group (p=0.74; Figure 7A). There was a large effect size for the changes in the amount of variability in the ankle plantarflexor torque for the MS group (d = 1.12) indicating that this change was likely a clinically meaningful change. Although not reaching significance, there also was a 26% increase in MVT (p=0.05; Figure 7B). The individual results for the CV of the ankle plantarflexor steady-state torque and MVT for the MS group are reported in the appendix materials (See Appendix A).

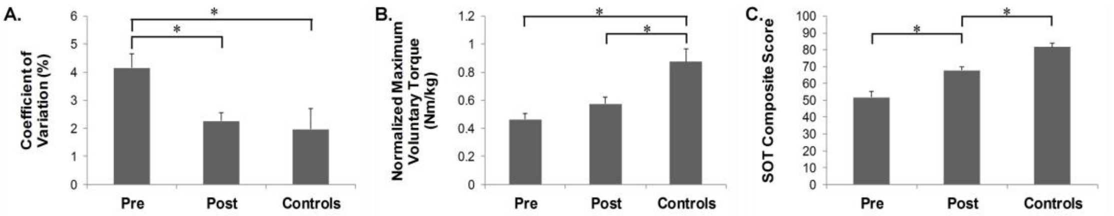

Figure 7: Pre/Post Results for Coefficient of Variation, Maximal Voluntary Torque, and SOT. A) Coefficient of variation (CV) of the ankle plantar flexor muscles before and after rehabilitation for the MS group and the CV for the control group. **B)** Normalized maximum voluntary torque before and after rehabilitation for the MS group and normalized maximum voluntary torque for the control group. **C)** SOT composite scores before and after rehabilitation for the MS group and the scores for the control group. ***** indicates p ≤ 0.03.

The composite SOT score increased by 30% following the rehabilitation training (p=0.001). Despite the notable increase in SOT composite scores, there was still a difference between the SOT composite scores of the MS group and the control group (p<0.001; Figure 7C). However, the 15.9 point increase in the mean SOT composite score is well above the 8.0 point increase needed to indicate a true treatment effect [156]. This notion is supported by the large effect size for the composite SOT score after training (d = 1.28). The individual results for the SOT for the MS subjects are reported in Appendix A.

There was a 15% increase in the preferred walking velocity (p=0.007; Figure 8A) and a 17% increase in the fast-as-possible walking velocity (p=0.007; Figure 8B). Even though the walking velocity for both speeds improved following training, participants were still slower than the control group (Preferred: p<0.001; Fast-as-possible: p<0.001).

A moderate effect size was seen for the improvements for both the preferred (d = 0.58) and the fast-as-possible walking velocities (d = 0.61). In addition to the faster walking velocities, there was a 15% increase in step length during the preferred pace ($p<0.001$; Figure 8C) and a 12% increase during the fast-as-possible pace ($p=0.004$; Figure 8D). However, these increases did not reach the step lengths seen in the control group (Preferred: $p<0.001$; Fast-as-possible: $p<0.001$). A moderate effect size was seen for the increased step length for both the preferred pace (d = 0.76) and the fast-as-possible pace (d = 0.64). There were no improvements in step width (Preferred: $p=0.487$; Fast-as-possible: $p=0.40$) or cadence (Preferred: $p=0.87$; Fast-as-possible: $p=0.16$) at either of the walking speeds. The results for both the preferred walking and fast-as-possible walking trials for the individual MS subjects are present in Appendix A.

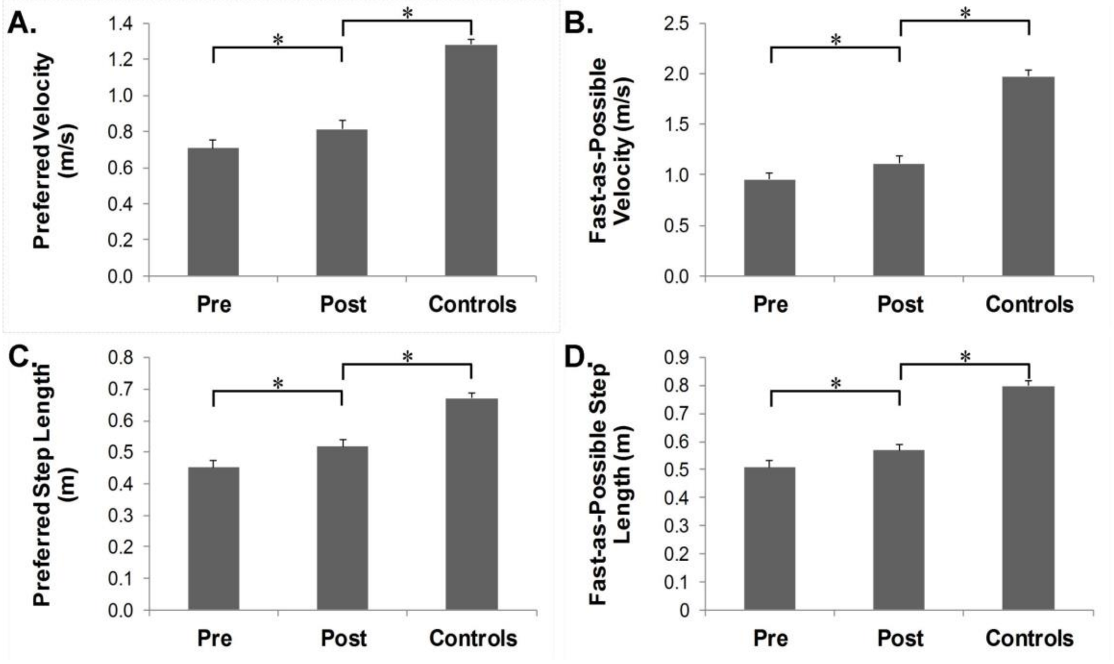

Figure 8: Pre/Post Results for Preferred and Fast-as-possible Walking Velocity and Step Length. **A)** Preferred walking velocity before and after rehabilitation for the MS group and the preferred walking velocity for the control group. **B)** Fast-as-possible walking velocity before and after rehabilitation for the MS group and fast-as-possible walking velocity for the control group. **C)** Preferred step length before and after rehabilitation for the MS group and the preferred step length for the control group. **D)** Fast-as-possible step length before and after rehabilitation for the MS group and the fast-as-possible step length for the control group. ***** indicates $p \leq 0.05$.

There was a significant, moderate negative correlation between CV and composite SOT composite score (r= -0.40; p=0.025). This correlation suggests that participants that had a higher SOT score tended to have less variability in their ankle plantarflexor force control. The CV was not correlated with any of the other measured outcome variables (p>0.05).

Discussion

This investigation involved a cohort of adults with MS who participated in an intensive neurorehabilitation protocol that lasted 14 weeks. Our results were promising because they showed that the participants had substantial improvements in their postural balance, mobility, strength, and control of the ankle plantarflexors. Altogether these exploratory results imply that the neurorehabilitation protocol employed in this investigation has potential to result in clinically relevant improvements in the motor performance of individuals with MS.

The higher CV of the steady-state torque control at baseline for individuals with MS indicates that these individuals had greater errors in their ability to match and sustain the target value with their ankle plantarflexors. However, after the neurorehabilitation protocol, these motor errors were markedly reduced and were not statistically different from the controls. This suggests that the neurorehabilitation protocol employed in this investigation improved and potentially normalized the motor control of the ankle plantarflexion musculature for many of the participants. Similar improvements in muscular control have been seen at the knee musculature of an elderly population following 20 weeks of Taiji training.[26] Taiji training is relatively similar to the rehabilitation protocol employed in this study because there is an emphasis on focusing one’s attention on balance and the ongoing sensory feedback about one’s posture. Although the specific neural adaptation for improved ankle plantarflexion force control cannot be determined from our data, we suspect that changes in variability of the motor unit discharge rates and/or changes in the synchrony of common motor units that serve the gastrocnemius and soleus musculature are possible mechanisms for this improvement.[85,128]

Following the neurorehabilitation protocol, the SOT composite score increased 15.9 points indicating that the amount of postural sway was reduced after rehabilitation. This change in composite score was well above the 8.0 improvement needed to attain a true treatment effect.[156] Moreover, seven of our MS subjects reached a post-intervention score of 70 or above, which is often reported as the cut-off for normal balance (See Appendix A). This indicates that almost half of our subjects had a normal postural sway after completing our neurorehabilitation program. The SOT has previously been used to identify the postural deficits of individuals with MS and the postural balance improvements following rehabilitation treatments.[57,69,70,79,152] The 15.9 point increase in composite scores was similar or greater to the improvements seen after individuals with MS participated in a 6-week vestibular rehabilitation program or home balance training program.[57,69] Therefore, the intensive combined therapeutic protocol employed in this investigation deserves further exploration because it may have a good potential to improve postural balance of individuals with MS.

There was a moderate negative correlation between the reduction of the errors in the steady-state ankle plantarflexion control and the amount of change in the postural sway after the neurorehabilitation protocol. This relationship infers that the individuals who had a greater improvement in their SOT score were likely to have greater reduction in the errors in their ankle plantarflexion force control. This finding provides further support for the clinical impression that impaired control of the ankle plantarflexors may be related to the poor postural control seen in individuals with MS.[13] We suspect that the remaining unexplained variance may be related to factors that were not measured in this investigation such as gastrocnemius spasticity, latency of the response of the ankle musculature to postural disturbances, and the muscular performance of the ankle dorsiflexors.[13,134] Alternatively, it has been noted that individuals with MS that have greater neuromuscular impairments tend to shift their postural control strategies from their ankle to the hip.[13,28] It is possible that some of the participants may have not effectively recalibrated their neuromuscular system to rely on the ankle for controlling their inherent postural sway and stabilization of their posture. Potentially, therapeutic strategies that are directed at teaching individuals with MS to relearn how to effectively use their ankle musculature for postural control may result in greater improvements in their balance.

Our results also displayed that the walking velocity during both the preferred and fast-as-possible trials improved, and these improvements were accompanied by longer step lengths. The increases in the gait velocity exceeded the improvements in gait velocity that were previously reported after an 8-week combined aerobic, resistance, and balance training protocol.[104] Therefore, the combination of gait and balance training positively influenced the mobility of individuals with MS. Despite the improved mobility, there was no correlation between the reduction of the errors in the steady-state ankle plantarflexion control and the amount of change of any of the measured mobility variables. This suggests that the steady-state control of the ankle plantarflexors was not a good predictor of the extent of the mobility improvements seen in many of the participants. A prior study has shown that the dynamic joint torques produced by the ankle during the stance phase of gait is improved after individuals with MS participate in an elliptical exercise program.[62] Potentially, the mobility improvements seen by our participants may be better reflected by changes in the ankle's dynamic torque production. Future investigations should challenge this notion by quantifying the dynamic torque production by the ankle during gait or during an isokinetic target matching task.

The therapeutic protocol utilized in this study was unique because it combined both gait and postural balance training into one therapeutic session. While both these types of training programs have been used for individuals with MS, they typically are implemented in isolation. Our therapeutic design was also unique because the participants focused on learning to adapt their movement strategies and were forced to use their impaired limbs which resulted in greater motor errors. Based on the neuroscience literature, this approach should drive beneficial neuroplastic changes for relearning a motor skill.[88] This approach is different from the more traditional compensatory approaches that have historically been used with individuals with MS, and is considerably different from the prior investigations that have focused on exercise alone. In addition, the therapeutic dosage was larger than what has been previously used with individuals with MS. Nevertheless, our therapeutic protocol is well aligned with the highly successful constraint-induced therapeutic paradigms that involve a high therapeutic dosage.[146] Given the clinically relevant outcomes presented in this investigation, future clinical trials should challenge the therapeutic dosage that is currently being used to improve the mobility and postural balance of individuals with MS.

Limitations

A major limitation of the current study was the lack of a group of individuals with MS completing the standard of care physical therapy to which the active group could be compared. Even though the current therapeutic protocol saw vast improvements in the balance and mobility of individuals with MS, it is unknown whether the improvements were due to the therapeutic dosage of the current study or the type of therapy being performed. Additionally, the sample size was relatively small, therefore, the generalizability of the outcomes are limited. Another limitation to the current study is the minimal amount of monitoring during the 12-week home program. Even with weekly phone contacts, a log book, and monthly visits, it is possible that the participants did not complete all the exercises or did not perform the exercises correctly. Future studies should address this limitation by providing the addition of a home visit by the physical therapist or intersperse the training with some of the sessions being performed in the clinic while under the guidance of a physical therapist.

Another limitation of our study is that spasticity of the plantarflexor muscles was not measured. It is well known that individuals with MS have increased spasticity. Therefore, the improvements in the motor control of the plantarflexors may have been due to a decrease in the overall muscle spasticity. Finally, it is possible that the level of impairment in the ocular and vestibular systems of the individuals with MS may have limited the improvements in the SOT scores for some of the participants. While the motor control of the ankle plantarflexor musculature was improved in the majority of the subjects, these improvements may have been negated by a higher level of impairment in the ocular or vestibular systems for some individuals.

Conclusion

The current study explored the influence of a novel neurorehabilitation protocol on the motor control of the ankle plantarflexor muscle of individuals with MS. Additionally it explored the influence this protocol had upon the balance and mobility of these individuals. After 14 weeks of intensive neurorehabilitation, individuals with MS achieved a normal amount of control during a submaximal isometric contraction with their ankle plantarflexors. Moreover, these individuals displayed a clinically significant change in their SOT scores which was related to the improvements in motor control of the plantarflexors. Finally, the individuals in the current study also displayed improvements in their mobility and plantarflexor muscle strength. Together, these improvements suggest that therapeutic protocols that target the ankle plantarflexors may be more effective in improving the balance of individuals with MS than other therapeutic protocols.

CHAPTER 4: TWO DIFFERENT TYPES OF HIGH-FREQUENCY PHYSICAL THERAPY PROMOTE IMPROVEMENTS IN THE BALANCE AND MOBILITY OF PERSONS WITH MULTIPLE SCLEROSIS

Introduction

Multiple sclerosis (MS) affects approximately 570,000 individuals in the United States, and is one of the most common neurologic disabilities in young and middle aged adults.[14,115] Persons with MS often face numerous motor impairments that have the potential to instigate postural balance and walking dysfunction.[13,20,90,116,120,126,134,139,140,147] Since postural balance and mobility are vital for daily living, they are often the primary focus of therapeutic goals. Traditionally, clinicians have discouraged persons with MS from participating in intensive exercise-based physical therapy programs because it was thought that these programs would exacerbate the MS symptoms.[122,141,144] However, the current therapeutic trends have been redirected towards identifying the optimal intensity and treatment parameters that result in improved mobility and postural balance.

Several investigations have attempted to address this current knowledge gap by evaluating the effectiveness of various types of programs for persons with MS such as balance specific or treadmill walking programs.[7,9,17,52,54,57,75,104,111,113,144,151] The outcomes of many of these investigations have reported improvements in postural balance and mobility. However, the therapeutic approaches used in these training programs have been highly variable in terms of frequency, intensity, and type. For example, these prior protocols have lasted between 2-13 weeks, with 2-3 treatment sessions per week that were anywhere from 15-60 minutes in length. This variability has blurred our understanding of the optimal parameters that will promote mobility and postural balance improvements in persons with MS.

We recently completed an exploratory investigation that evaluated if a novel, high-frequency physical therapy protocol can augment clinically relevant improvements in the postural balance and mobility of persons with MS.[36] The protocol was performed twice-a-day, for five days-a-week over 14 weeks. This high frequency was selected based on the success of the immersive constraint-induced therapeutic protocols used with stroke patients.[146] Our training program was also unique because it was directed at improving the individual's motor adaptability by constantly challenging the patient's postural balance and mobility. During the exercises, the therapist would provide verbal feedback to direct the patient's attention towards exploring new ways to optimally adapt to the challenging task demands. The results from this exploratory study were very promising and showed vast improvements in postural balance, preferred and fast-as-possible walking speed, and control of the ankle musculature.

We suspect that the motor adaptation exercises used in our preliminary study were essential to our successful outcomes because the individual's attention was focused towards increasing awareness of their motor strategies, and re-learning how to meet the task demands. We suggest that this treatment approach was optimal because it promoted a greater amount of variability in the practiced motor tasks, which has been shown to potentially augment beneficial neuroplastic changes in the brain.[88,157] Based on these premises, we anticipate that a high-frequency therapeutic protocol that utilizes traditional exercises may achieve less favorable results in persons with MS. The purpose of this exploratory investigation was to test this notion by evaluating the mobility and postural balance improvements that could be achieved in a cohort of persons with MS who participated in a therapeutic exercise protocol, and a cohort of persons with MS who participated in our motor adaptation protocol. We hypothesized that the cohort that completed the motor adaptation therapeutic protocol would have greater improvements in postural balance, preferred walking speed, and walking endurance than the cohort who completed the therapeutic exercise protocol.

Methods

Based on our initial investigation, 12 persons with MS would provide greater than 80% power to detect differences at a 0.05 alpha level. Assuming a 20% dropout rate, we aimed to recruit at least 14 persons to participate in each group. The participants were recruited from the University of Nebraska Medical Center's (UNMC) Multiple Sclerosis Clinic with the following inclusion criteria: between 30-70 years old, a Kurtzke Expanded Disability Status Score (EDSS) of 3.0-6.5, a definitive diagnosis of MS, able to walk on a treadmill at a minimum speed of 0.5 miles per hour while holding onto handrails, cognitively competent, and a Mini-Mental State Examination score of >21. The exclusion criteria were: documented MS-related relapse in the previous six months, major MS-specific medication changes in the previous three months, and the presence of another major co-morbidity such as neurological disorders, uncontrolled pain, hypertension and diabetes. The study was reviewed and approved by the UNMC Institutional Review Board, and all participants provided written consent. The participants were pseudo-randomly assigned to either a motor adaptation cohort (MAC) or a therapeutic exercise cohort (TEC) upon enrollment. The pseudo-random assignments were performed such that a participant meeting the inclusion criteria was randomly assigned to one of the treatment groups, and a second participant with a similar EDSS was placed in the other group. The enrolled subjects completed all outcome measures before and after their respective therapeutic programs.

Interventions

The total intervention period for both cohorts was six weeks. The therapy was performed twice a day for five consecutive days each week. The initial two weeks were conducted on the UNMC campus under close supervision of a physical therapist (HR, KV). The remaining four weeks were performed by the patient at their home and were monitored weekly via teleconferences with the therapist. Subjects completed the same activities at home as they did during the initial two weeks and kept a home exercise program log book to track their activity.

Motor Adaptation Cohort

The procedures for our MAC program were the same as what we previously reported.[26] The initial five minutes of each session began with a warm-up of isolated trunk and limb movements focused on control, as well as individual-specific stretches and coordination activities for the limbs. Next, the subjects completed a 20 minute balance training program that consisted of tasks such as standing in the corner with their feet on a piece of foam with eyes closed. Each training session concluded with 20 minutes of treadmill and overground walking. The treadmill training consisted of activities such as walking backward or sideways. The overground training activities varied in walking direction, speed, and/or use of assistive device. Difficulty level was steadily increased both within and between sessions for all activities. The therapist provided verbal feedback to direct the patient’s attention towards monitoring the outcomes of their motor performance, and exploring new ways to adapt to the challenging tasks.

Therapeutic Exercise Cohort

The activities in the TEC program were similar to those that would be performed in a traditional group exercise program. Each session consisted of 15 minutes of strength and flexibility exercises, 15 minutes of postural balance exercises, and 15 minutes of treadmill walking. Strength exercises included things such as forward/backward lunges and squats. The flexibility training focused specifically on the lower extremities. Balance activities consisted of static balance exercises, such as standing on one leg as long as possible with support. The subjects were allowed to adjust their speed on the treadmill as needed to accomplish the total time and were encouraged to remove one or both hands from the handrails, if possible. Compensatory strategies (i.e., widening the base of support) for completing the assigned exercises were demonstrated when subjects were having difficulty completing the tasks.

Postural Control Measures

Postural control was assessed using the composite score on the sensory organization test (SOT) (NeuroCom® International, Clackamas OR, USA), which consists of six conditions that measure each subject’s ability to integrate visual, somatosensory, and vestibular feedback to reduce the overall amount of postural sway. The composite score was calculated by the NeuroCom software based on the subject’s overall amount of postural sway, which was measured with a force plate integrated into the system’s platform. A higher composite score indicated a lower amount of postural sway and better balance.

Mobility Measures

Subjects were allowed to use their regular assistive devices (i.e., canes, wheeled walkers, ankle foot-orthoses) for all mobility measures.

Walking Endurance

Walking endurance was measured using the 6-minute walk test. Subjects walked back and forth around cones that were placed at the ends of a ~40 meter hallway, and were instructed to try to walk as far as they possibly could within the six minute time limit. No verbal encouragement was provided during the test, and the subjects were allowed to stop for rest during the test, but the time was not paused.

Walking Speed and Spatiotemporal Kinematics

The spatiotemporal kinematics of gait were measured with a digital mat (GAITRite®, CIR Systems Inc., Sparta, NJ). The participants completed two self-paced walking trials, and the two trials were averaged together for the final statistical analyses. The variables of interest were gait velocity (meters/second), step width (meters), step length (meters), and cadence (steps/minute).

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics 22 statistical software (IBM Corp., Armonk, NY, USA). Separate mixed repeated measures ANOVAs (Group x Pre/Post Assessment) were used to compare the differences of the variables of interest between therapeutic groups and before/after the therapeutic protocols. Cohen's d was calculated to determine the effect sizes of the respective changes. The following guidelines were used to interpret the effect sizes: 0.2 is a small effect size, 0.5 is a moderate effect size, and 0.8 is a large effect size.[30] The alpha level of 0.05 was used to interrogate all data for statistical significance. The data in the text is reported as the mean ± standard error of the mean of the data.

Results

Forty-two individuals were initially screened for eligibility to participate in the study (Figure 9). From this initial screening, 32 persons with relapsing-remitting or secondary progressive MS fit the inclusion criteria and were assigned to either group (See Table 5 for Subject Characteristics). All subjects were blinded as to which therapeutic intervention cohort that they were assigned. In the MAC, two subjects were withdrawn from the study due to non-compliance to the study procedures, and one individual discontinued due to a non-MS related health complication. In the TEC, one individual discontinued due to a non-MS related health condition, and one individual discontinued due to a fall-related injury that occurred during the training program. At the end of the intervention period, 14 individuals in the MAC (Mean Age: 53.9±8 years, 12 Females; EDSS = 5.4±0.2) and 13 individuals in the TEC (Mean Age: 54.8±9 years, 7 female; EDSS = 5.3±0.2) completed the entire six weeks of their respective programs and were included in the analyses. No adverse MS-related events occurred during the intervention period for any subject who completed the programs.

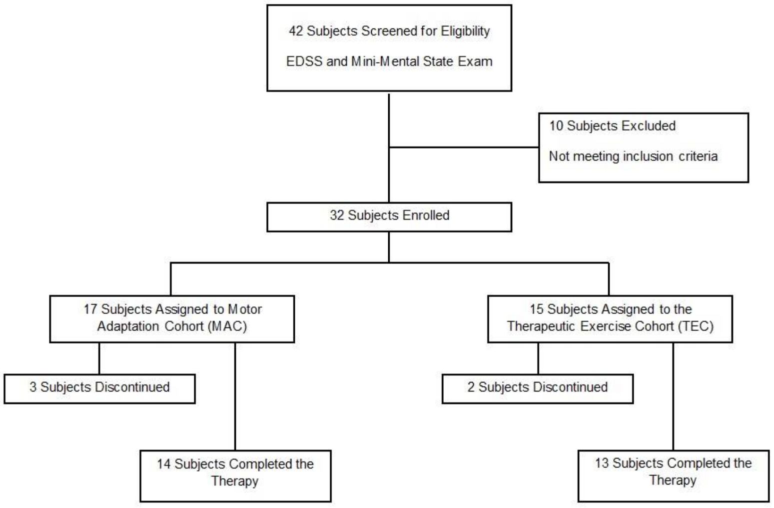

Figure 9: Flow Diagram of Participant Recruitment and Participation.

Table 5. Baseline Demographic and Clinical Characteristics of the Participants

Therapeutic Exercise Cohort (TEC)

TEC Subject	Gender	Age (Years)	MS Type	MS Duration	EDSS Score	Assistive Device
1	Male	69	RR	24	5.0	Cane/AFO
2	Male	48	SP	12	5.5	Cane
3	Female	57	RR	12	5.5	Three Foot Cane
4	Female	57	RR	12	4.0	None
5	Female	36	SP	14	6.5	Walker
6	Male	55	SP	4	4.5	AFO
7	Male	59	RR	5	6.0	AFO
8	Male	65	SP	7	6.5	Walker
9	Female	50	RR	15	4.5	Cane
10	Female	50	RR	12	3.5	None
11	Female	60	RR	15	5.0	Cane
12	Male	64	RR	10	6.0	Cane
13	Male	56	RR	19	6.0	Bioness and Cane
14	Male	40	RR	8	6.0	Cane/AFO
15	Female	56	RR	9	5.0	None
Average	**7 Female**	**54.8 ± 9**	**11 RR**	**11.9 ± 5**	**5.3 ± 0.2**	

Motor Adaptation Cohort (MAC)

MAC Subject	Gender	Age (Years)	MS Type	MS Duration	EDSS Score	Assistive Device
1	Female	44	RR	17	4.0	None
2	Female	43	RR	11	6.0	Cane
3	Female	55	RR	30	4.0	None
4	Male	68	SP	9	6.0	Cane/AFO
5	Male	49	RR	12	5.5	AFO
6	Male	54	SP	18	5.5	None
7	Female	43	RR	12	6.0	Cane
8	Female	47	RR	17	6.5	Forearm Crutches
9	Male	61	RR	15	5.5	Cane/AFO
10	Female	66	RR	10	6.0	Cane
11	Female	45	RR	8	4.0	None
12	Male	59	SP	13	6.0	Cane/AFO
13	Female	42	RR	27	6.5	Walker/AFO
14	Female	60	SP	18	6.0	Cane
15	Female	59	SP	21	3.5	Cane
16	Female	62	SP	12	4.0	None
17	Female	59	RR	21	6.5	Walker
Average	**12 Female**	**53.9 ± 8**	**11 RR**	**15.9 ± 6**	**5.4 ± 0.2**	

Abbreviations. MS, multiple sclerosis; RR, relapsing-remitting multiple sclerosis; SP, secondary progressive multiple sclerosis; AFO, ankle foot orthosis.

Postural Control Measures

There was a significant Pre/Post main effect for the SOT composite score (p=0.001; Cohen’s d = 0.88; Figure 10A) indicating that there was an improvement in the postural balance of both groups. Both groups improved their postural balance by 24.1%.

However, there was not a significant interaction or group main effect (ps>0.05), suggesting that both groups improved their postural balance similarly.

Mobility Measures

Walking Endurance

There was a significant Pre/Post main effect for the 6-minute walk test (p=0.002; Cohen’s d = 0.39; Figure 10B), indicating that both groups improved their walking endurance. Collectively, both groups had a 12.9% increase in their walking endurance. Despite this main effect, there was not a significant interaction or group main effect (ps>0.05), indicating that both groups improved their walking endurance equally.

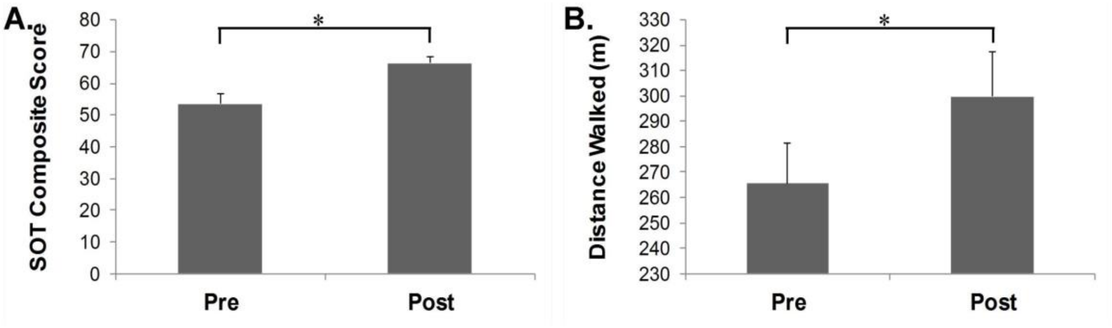

Figure 10: Pre/Post Results for SOT and 6-Minute Walk Test. A) The Pre/Post Assessment Main Effect for the Sensory Organization Test Composite Score. **B)** The Pre/Post Assessment Main Effect for the 6-minute walk test. * indicates p<0.05.

Preferred Walking Speed

There was a significant Pre/Post main effect for the walking velocity (p=0.004; Cohen’s d = 0.42; Figure 11A), demonstrating that both groups improved their preferred walking speed. Overall both groups had an 11.7% increase in the walking velocity. There was not a significant interaction or group main effect (ps>0.05), which indicated that both groups had similar improvements in their walking speed.

Spatiotemporal Kinematics

There was a significant Pre/Post main effect for the step length (p<0.001; Cohen's d = 0.55; Figure 11B), signifying that both groups used a longer step length after completing the respective therapeutic protocols. Overall both groups had a 10.2% increase in the step length. There was no group main effect (p>0.05); yet, there was a significant Group x Pre/Post Assessment interaction (p=0.042; Figure 11C). Our post-hoc analysis indicated that there were no differences in the step lengths of the respective groups during at baseline or after the therapy (ps>0.05). After completing their respective therapeutic protocols, the MAC improved their step length by 16.4% (p=0.001; Cohen's d=0.73) and the TEC improved their step length by 6.0% (p=0.001; Cohen's d=0.36).

There were no significant main effects or interactions for step width and cadence suggesting neither protocol influenced these kinematic variables (ps>0.05).

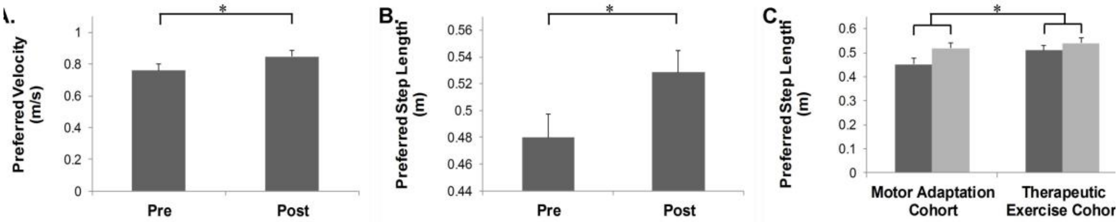

Figure 11: Pre/Post Results for Preferred Walking Velocity and Step Length. A) The Pre/Post Assessment Main Effect for the velocity at the self-selected preferred walking pace. **B)** The Pre/Post Assessment Main Effect for the step length at the self-selected preferred walking pace. **C)** The Group x Pre/Post Assessment Interaction for the step length at the self-selected preferred walking pace. The dark grey bars represent the mean step lengths before the intervention period. The light grey bars represent the mean step lengths after the intervention period. * indicates p<0.05.

Discussion

Our prior investigation suggested that a high frequency of physical therapy exercises that focused on motor adaptation has the potential to promote clinically meaningful improvements in the postural balance and mobility of persons with MS.[36] In this investigation, we tested this notion comparing the results from a cohort of persons with MS who participated in our motor adaptation physical therapy protocol with a cohort of persons with MS who participated in a therapeutic exercise protocol. We hypothesized that the participants in the MAC would have greater improvements in postural balance, preferred walking speed, and walking endurance than the participants in the TEC. Our results showed that both groups made significant improvements in their postural balance and mobility. However, our hypothesis was not supported because there were no differences in the extent of the improvements seen between the respective treatment groups. Since both groups completed different activities at the same high frequency, the frequency of physical therapy might be important for promoting improvements in persons with MS.

Both groups had a 13 point improvement in their SOT scores, which was well above the 8.0 point criteria for a clinically meaningful change but is somewhat lower than what has been reported from prior investigations (16-18 points).[9,57,156] These other studies utilized 12 one-hour balance treatment sessions over a 4-6 week period under the direction of a physical therapist, which was considerably different than the dosage employed in the current investigation. We suspect that the hour of focusing on task specific postural balance training utilized in the prior studies may have augmented the larger postural balance improvements. Secondarily, we suspect larger balance improvements may have been achieved if our subjects would have continued to work one-on-one with the physical therapist for all of the treatment sessions.

Surprisingly, there were no differences in the postural balance improvements between the respective groups. These outcomes were contradictory to our original hypothesis and imply similar outcomes can occur when the program is less focused on re-learning how to adapt to the challenging postural conditions. Perhaps the balance exercises used in the TEC provided enough challenge to direct the individual's attention towards relearning how to maintain their balance. Also, the outcomes were possibly equivocal because the exercises that the TEC were assigned were more feasible for them to complete at home, whereas the MAC may have had greater difficulty in properly adjusting the difficulty level of the balance exercises without the one-on-one interaction with the therapist. This may have resulted in the at-home balance protocol being somewhat similar for both groups.

After completing the respective therapeutic protocols, both groups had improvements in their mobility including better walking endurance and faster walking speed, which was accomplished by using a longer step length. However, the therapeutic outcomes of the respective groups were equivocal indicating that both treatment approaches may have the same effect on the mobility of persons with MS. These improvements in the mobility of our subjects could be related to the high frequency of walking activities that both groups completed. The treatment protocols used in other treadmill training investigations that have used preferred walking speed as an outcome variable have consisted of 30 minutes of treadmill walking that was performed 3 times a week, over a 4-week period.[7,111] The outcomes from these prior studies have been quite variable with a 3-12% improvement in walking speed. Our results are at the ceiling of what has been previously reported, which suggests that a higher frequency of walking activities may be beneficial for improving the mobility of persons with MS.

Overall the positive results following the intervention period in both groups suggest that high-frequency physical therapy may promote improvements in the postural balance and mobility of persons with MS. The frequency of physical therapy used in this investigation was much higher than the majority of exercise or physical therapy programs that have been evaluated for persons with MS.[7,9,17,52,54,57,104,111,151] A recent investigation by Kalron and colleagues[75] consisted of a 3-week rehabilitation program that was comprised of many different exercise types which were performed 5 days-a-week. Their results demonstrated that a high amount of activity and physical therapy can result in improved mobility in persons with MS.[75] These results further support the notion that a high frequency of physical therapy may be an important parameter for promoting improvements in the mobility of persons with MS. This conjecture should be challenged by future studies directed at identifying the optimal treatment parameters for persons with MS.

Limitations

This study was limited due to the small sample size of each cohort. Potentially by having more subjects in each group, the improvements in postural balance and mobility within each group could have been augmented, allowing for stronger comparisons between groups. An additional limitation to the study was the lack of a group who completed a physical therapy program for individuals with MS conducted at a more normal dosage level. This would allow for better insight to be gained as to whether the frequency of the therapy is an important parameter for promoting the balance and mobility improvements seen in the current study.

Conclusions

In conclusion, our exploratory results suggest that the focus of the physical therapy may not be the key factor for promoting improvements in the postural balance and mobility of persons with MS. Our results appear to imply that high-frequency physical therapy may be an important dosage parameter for improving the postural balance and mobility of persons with MS. These insightful preliminary outcomes should be further explored and taken into consideration when deciding on dosage parameters that will likely meet the therapeutic goals of persons with MS.

CHAPTER 5: INDIVIDUALS WITH MULTIPLE SCLEROSIS EXHIBIT MORE REGULAR TRUNK ACCELERATIONS AFTER PHYSICAL THERAPY

Introduction

Multiple sclerosis (MS) is a progressive, demyelinating disease that is typically diagnosed in adults who are between the ages of 20-40 years old.[14] The demyelination affects both the sensory and motor pathways, which disrupts balance and can also affect one's mobility. Walking ability has been reported as being the most important functional ability to individuals with MS and about 50% of all individuals with MS will become reliant upon some sort of assistive device within their lifetime.[58,149] Additionally, about 52% of individuals with MS report falling within the past 6 months.[48] Individuals with MS may adopt compensatory strategies during walking in order to address this instability and their increased fear of falling. These compensatory strategies may include shorter step lengths, slower walking velocities and cadences, and wider step widths.[5,97,119]

Individuals with MS also tend to have more variability in their gait patterns. Previous investigations have displayed higher amounts of variability than healthy adults in step timing, step lengths and widths, and the percentage of the gait cycle spent in double or single support during walking in people with MS.[132,133,136] Additionally, individuals with MS have greater joint angle variability at the ankle, knee, and hip joints than healthy adults.[32] This gait variability has been seen to scale with disability level and the use of assistive devices. These increases in the variability of the gait patterns of individuals with MS may be due to an increase of noise within the neuromuscular system or alterations to the musculature of the lower extremities such as muscle strength or spasticity. Similar increases in gait variability have been observed in other clinical and elderly populations.[8,37,56,106] These previous investigations have also identified relationships between the amount of variability in gait and disability, such as risk of falling. Therefore, this increase in variability in the gait patterns of individuals with MS may contribute to the higher percentage of falls and decreased mobility reported by these individuals.

In addition to the increased variability of the gait patterns of individuals with MS, there may also be an altered amount of variability in the trunk accelerations of these individuals during walking. The trunk is an important control aspect of walking because it contains about 2/3 of the body's weight and is located at about 2/3 of the body's height from the ground.[155] Stabilization of the trunk during walking is vital to achieving dynamic balance and also stabilization of the head. Accelerometry has been used to explore the gait of healthy adults, the elderly, and numerous clinical populations.[41,66,67,80,96,98,101] Recently, a small number of investigations have also explored the trunk accelerations of individuals with MS during short walking distances using both linear and non-linear techniques to quantify variability.[59,61,138] Linear techniques are able to quantify the amount of variability present within the acceleration pattern, while nonlinear techniques can provide insight into the time dependent changes in the movement. Huisinga et al.[61] used linear techniques, such as root mean square, and nonlinear techniques, such as Lyapunov exponents, to explore the variability and structure of the mediolateral and antero-posterior trunk accelerations of both healthy adults and individuals with MS during a 30 second walking trial. The individuals with MS actually displayed normal or lower amounts of trunk acceleration variability but had more divergence in both directions suggesting that the trunk accelerations of individuals with MS are less periodic. Less periodic and more divergent patterns may indicate a lower amount of dynamic stability and have been related to an increased risk of falling. Therefore, it appears that individuals with MS may exhibit less periodic patterns in their trunk accelerations, which potentially reflects the compensatory strategies adopted by individuals with MS during walking.

Even though it appears that individuals with MS have less periodic patterns in their trunk accelerations, it is currently not known whether the trunk acceleration variability can be improved with therapeutic interventions. Previous investigations have observed improvements in step lengths and walking velocity after various therapeutic programs such as strength training, treadmill training, and yoga.[36,53,54,104,111] Additionally, walking endurance has also been improved following similar interventions.[7,111] Since it has been proposed that shorter step lengths and slower walking velocities are compensatory strategies employed by individuals with MS due to an increase in instability, it is possible that improvements in trunk acceleration variability may also occur following therapeutic interventions. These improvements in trunk acceleration variability could promote improved stabilization of the trunk, thus potentially allowing for the adoption of a more normal walking pattern.

The purpose of this investigation was to explore the influence of a therapeutic exercise intervention upon the variability of the resultant trunk acceleration of individuals with MS. Sample Entropy (SampEn) was used to quantify the regularity of the acceleration time series before and after the therapeutic intervention period. A higher SampEn suggests that a time series is less regular; whereas a lower SampEn suggest a more regular time series. Standard deviation (SD) was used to quantify the amount of variability present in the acceleration signal; a higher SD suggests a signal is more variable. We hypothesized that individuals with MS would have a higher SampEn than healthy adults before the therapeutic intervention but that the SampEn would significantly decrease after the intervention period. It was also hypothesized that individuals with MS would have a lower SD than healthy adults before therapy but the SD would significantly increase after the intervention period. Secondarily, we interrogated the influence of the therapeutic intervention upon the spatiotemporal gait kinematics and walking endurance of individuals with MS. We hypothesized that the spatiotemporal kinematics and walking endurance would be improved after the therapeutic intervention and that these improvements would be related to the improvements in trunk acceleration variability.

Methods

Fifteen individuals (7 female; mean age: 54.8 ± 9; see Table 6 for subject characteristics) with relapsing-remitting or secondary progressive MS were enrolled in this study. The participants were recruited from the University of Nebraska Medical Center's (UNMC) Multiple Sclerosis Clinic with the following inclusion criteria: between 30-70 years old, a Kurtzke Expanded Disability Status Score (EDSS) of 3.0-6.5, a definitive diagnosis of MS, able to walk on a treadmill at a minimum speed of 0.5 miles per hour while holding onto handrails, cognitively competent, and a Mini-Mental State Examination score of >21. The exclusion criteria were: documented MS-related relapse in the previous six months, major MS-specific medication changes in the previous three months, and the presence of another major co-morbidity such as neurological disorders or uncontrolled pain, hypertension, and diabetes. Fifteen healthy, age-matched adults (10 female; mean age: 53.5 ± 7 years) were also enrolled and acted as a control group. The control group subjects were free from any known orthopedic or neurological impairments. All experimental procedures were reviewed and approved by the UNMC Institutional Review Board. All subjects provided written informed consent before participating in the experimental procedures. The enrolled subjects with MS completed all outcome measures before and after the therapeutic intervention and the control subjects completed all outcome measures once.

Table 6. Baseline Demographic and Clinical Characteristics of the Participants

Subject	Gender	Age (Years)	MS Type	MS Duration	Assistive Device
1	Male	69	RR	24	Cane/AFO
2	Male	48	SP	12	Cane
3	Female	57	RR	12	Three foot cane
4	Female	57	RR	12	None
5	Female	36	SP	14	Walker
6	Male	55	SP	4	AFO
7	Male	59	RR	5	AFO
8	Male	65	SP	7	Walker
9	Female	50	RR	15	Cane
10	Female	50	RR	12	None
11	Female	60	RR	15	Cane
12	Male	56	RR	19	Bioness & Cane
13	Male	64	RR	10	Cane
14	Male	40	RR	8	Cane/AFO
15	Female	56	RR	9	None
Average	7 Female	54.8 ± 9	11 RR	11.9 ± 5	

Abbreviations: MS, multiple sclerosis; RR, relapsing-remitting multiple sclerosis; SP, secondary progressive multiple sclerosis; AFO, ankle foot orthosis

Therapeutic Exercise Intervention

The total intervention period was six weeks. The therapy was performed twice a day for five consecutive days each week. The initial two weeks were conducted on the UNMC campus under close supervision of a physical therapist (HR, KV). The remaining four weeks were performed by the patient at their home and were monitored weekly via teleconferences with the therapist. Subjects completed the same activities at home as they did during the initial two weeks and kept a home exercise program log book to track their activity.

Each therapy session consisted of 15 minutes of strength and flexibility exercises, 15 minutes of postural balance exercises, and 15 minutes of treadmill walking. The activities selected for the therapeutic program were similar to those that would be performed in a group exercise program. Strength exercises included things such as forward/backward lunges, stepping up/down a step, and squats. Flexibility training was completed both standing up and laying down on a mat. Subjects were shown how to stretch the lower extremity muscles; especially any muscle that was specifically problematic to a participant. Both static and dynamic balance exercises were completed in each session. Static balance exercises included standing on a piece of foam with eyes open and feet wide apart of standing or one leg as long as possible with support. Dynamic balance exercises included stepping over small obstacles, walking sideways, or walking heel to toe. While walking on the treadmill, the subjects were encouraged to remove one or both hands from the handrails if possible. The subjects were allowed to increase and decrease their speed as needed to accomplish the total time.

6-Minute Walk Test

All subjects completed a 6-minute walk test in a hallway ~40 meters long. Subjects walked back and forth around cones that were placed at the ends of the hallway and were instructed to try to walk as far as they possibly could within the six minute time limit. No verbal encouragement was provided during the test. The subjects with MS were allowed to use their regular assistive devices (see Table 6) during the test. Accelerations of the trunk were measured during the 6-minute walk test using a tri-axial accelerometer (Delsys Inc., Natick, MA, USA) that was positioned over the L2 vertebra and attached to a neoprene belt which was tightly wrapped around the subject's lower trunk. The accelerometer signal was streamed wirelessly to a computer through a custom LabView program (1000 Hz; National Instruments Inc., Austin, TX, USA).

The unfiltered resultant accelerometer signal was analyzed using a custom MatLab program (The Mathworks, Inc., Natick, MA, USA). The resultant accelerometer signal was evaluated in this study to account for any differences in the placement of the accelerometer at the different time points. The first and last 30 seconds of the 6-minute walk test were removed from the analysis in order to ensure the signal primarily included steady-state walking. SD was used to quantify the amount of variability present in the accelerometer signal. A higher SD suggests the signal has a greater amount of variability within it. SampEn was used to measure the regularity in the resultant accelerometer signal time series.[121] SampEn identifies and counts the number of self-similar vectors at length m and m+1 where m is the number of points compared. For our analysis, we compared two points (m=2), the similarity criterion was 20% of the standard deviation of the signal (r = 0.2), and our time lag was 102 (tau = 102). The time lag was selected using the Average Mutual Information algorithm.[1] A more regular time series will have a SampEn closer to zero, while a completely irregular time series with have a SampEn that approaches infinity.

Spatiotemporal Gait Kinematics

The subjects with MS completed two self-paced walking trials where the spatio-temporal kinematics of gait were measured with a digital mat (GAITRite®, CIR Systems Inc., Sparta, NJ). These two walking trials were averaged together for the final statistical analyses. The variables of interest were gait velocity (meters/second), step width (meters), step length (meters), and cadence (steps/minute).

An eight camera three-dimensional motion capture system (120 Hz; Vicon, Centennial, CO, USA) was used to evaluate the spatiotemporal gait kinematics of the control group. A modified Helen Hayes reflective marker set was placed bilaterally on the lower extremities of each subject. Subjects completed three self-paced walking trials. Walking velocity (meters/second) was calculated based on the trajectory of a marker placed upon the pelvis. Step length (meters), step width (meters), and cadence (steps/minute) were calculated using the trajectories of the heel marker on each foot. The differences between methodologies used to evaluate the spatiotemporal kinematics of gait for each group should not have influenced the results because a high degree of similarity for the measurements of gait parameters has been seen between the digital mat and motion capture data.[148]

Statistical Analyses

All statistical analyses were performed using IBM SPSS Statistics 23 statistical software (IBM Corp., Armonk, NY, USA). The changes in the SD, SampEn, 6-minute walk test, and spatiotemporal gait kinematics after the therapeutic intervention were interrogated using paired t-tests. The difference between the groups in the distance walked during the 6-minute walk test, the SD, the SampEn, and spatiotemporal gait kinematics was interrogated using independent samples t-tests. Pearson correlation coefficients were calculated between the percent change in the variability measures and the percent changes in the gait measures. An alpha level of 0.05 was used to interrogate all data for significance. The data is reported as the mean ± standard error of the mean.

Results

Thirteen subjects completed the entire six weeks of the therapeutic intervention. One individual discontinued due to a non-MS related health condition and one individual discontinued due to a fall-related injury that occurred during the therapeutic program. No adverse MS-related events occurred during the intervention period for any of the subjects that completed the program. All subjects who completed the program are included in all analyses.

6-minute Walk Test

After the therapeutic exercise program, there was a significant improvement in the distance walked during the 6-minute walk test (Pre: 298.8 ± 23 m; Post: 318.0 ± 24 m; $p = 0.04$). The control group walked significantly farther in the 6-minute walk test than the group with MS at either time point (Controls: 505.3 ± 18 m; ps < 0.001). Before the therapeutic program, the individuals with MS had a lower SD than the control group indicating that there was a lower amount of variability in the trunk accelerations of the subjects with MS (p = 0.004; Figure 12A). There was a significant increase in the SD after the therapeutic program (p = 0.008; Figure 12A) indicating that there was more variability in the trunk accelerations after the intervention. However, the subjects with MS still had a significantly lower post-intervention SD than the control group (p = 0.03; Figure 12A). Before the therapeutic program, the individuals with MS had a higher SampEn than the control group indicating that the acceleration time series of the individuals with MS was less regular than the control group (p < 0.001; Figure 12B). There was a significant decrease in SampEn for the group with MS after the therapeutic program (p = 0.01; Figure 12B) suggesting that the acceleration time series of the individuals with MS became more regular after the intervention. However, the subjects with MS still had a significantly higher post-intervention SampEn than the control group (p = 0.01; Figure 12B).

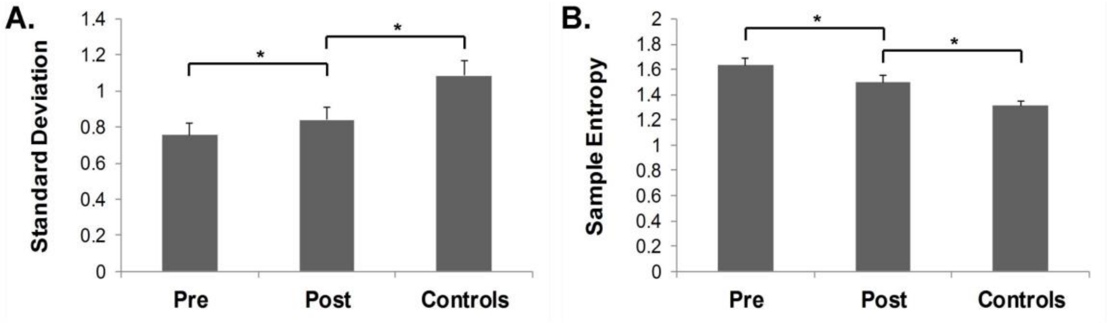

Figure 12: Standard Deviation and Sample Entropy Results. A) The standard deviation of the resultant accelerations during the 6-minute walk test of the individuals with MS before and after the therapeutic intervention and the standard deviation of the control group. This graph displays that the individuals with MS significantly increased the amount of variability in their trunk accelerations after the intervention but still had a reduced amount of variability when compared to the control group. **B)** The sample entropy of the resultant accelerations during the 6-minute walk test before and after the therapeutic intervention by the group with MS and the for the control group. This graph displays that after the completion of the therapeutic intervention, the individuals with MS had more regular accelerations but still displayed less regular accelerations than the control group. * indicates $p < 0.05$.

Spatiotemporal Gait Kinematics

After the therapeutic intervention, the subjects with MS significantly improved their walking velocity (Pre: 0.83 ± 0.06 m/s; Post: 0.90 ± 0.06 m/s; p = 0.05) and step length (Pre: 0.51± 0.02 m; Post: 0.54 ± 0.02 m; p = 0.03). There was an 8% increase in walking velocity and a 6% increase in step lengths. After the intervention, the subjects with MS still walked significantly slower than the control group (Controls: 1.17 ± 0.02 m/s; $p < 0.001$) but they did normalize their step lengths to that of the control group (Controls: 0.58 ± 0.01 m/s; $p = 0.11$). There were no changes in step width (Pre: 0.14 ± 1 m; Post: 0.14 ± 2 m; $p = 0.52$) or cadence (Pre: 96.9 ± 4 steps/min; Post: 99.6 ± 4 steps/min; $p = 0.20$). There was no significant difference between the step width between groups at any time point (Controls: 0.17 ± 0.01 m; ps > 0.05) and the individuals with MS had a significantly slower cadence than the control group at all time points (Controls: 117.6 ± 3 steps/min; ps < 0.001).

Correlations

There was a negative correlation between the percent change in SampEn and the percent change in the distance walked during the 6-minute walk test ($r = -0.64$; $p = 0.02$). This indicates that the subjects who had a greater improvement in the distance walked after the therapeutic intervention also exhibited a greater improvement in the regularity of the accelerometer signal time series. There was a negative correlation between the percent change in SampEn and the percent change in the walking velocity ($r = -0.56$; $p = 0.05$) indicating that the subjects who exhibited a greater improvement in walking speed after the therapeutic intervention also had a greater improvement in the regularity of the accelerometer signal time series. Finally, there was a negative correlation between the percent change in SampEn and the percent change in the cadence ($r = -0.68$; $p = 0.01$) which indicates that the individuals who had greater improvements in their cadences also had greater improvements in the regularity of their acceleration time series. There were no significant correlations between the percent change in the SD and the improvements in the gait measures (ps > 0.05).

Discussion

The purpose of this study was to determine whether a therapeutic exercise intervention would promote improvements in the variability of the resultant trunk accelerations of individuals with MS during walking. We hypothesized that individuals with MS would exhibit a lower amount of trunk acceleration variability and less regular trunk accelerations before participating in the therapeutic exercise intervention but that the amount of variability would increase and the accelerations would become more regular following the completion of the program. Moreover, we hypothesized that these improvements in the regularity of the trunk accelerations would be related to improvements in the spatiotemporal gait kinematics and walking endurance. Our results showed that the individuals with MS who completed the therapeutic protocol walked further during the 6-minute walk test, walked at a faster velocity, took longer step lengths, had a higher amount of variability in their trunk accelerations, and also exhibited more regular trunk accelerations. Moreover, the improvement in the regularity of the trunk accelerations was strongly related to the improvements in walking endurance, velocity, and cadence.

The outcomes from our study suggested that individuals with MS have less regular trunk accelerations than their healthy age-matched cohorts. Moreover, our results indicated that individuals with MS have decreased amounts of variability in their trunk accelerations. These results are similar to those found in previous investigations which identified that individuals with MS have less trunk acceleration variability which is more periodic in nature.[61] The culmination of these findings suggests that individuals with MS have abnormal structure to their trunk accelerations, which possibly promotes instability during walking in these individuals. Stabilization of the trunk is important for maintaining visual control during walking.[101] Individuals with MS potentially rely more heavily upon vision for the maintenance of balance during walking due to impairments in the somatosensory and vestibular systems caused by MS.[109] Moreover, individuals with MS appear to increase the amplitude and magnitude of their postural responses because of decreases in somatosensory conduction.[13] Therefore, the less regular trunk accelerations may reflect a disruption in the proper integration of the visual and somatosensory information that are vital for maintaining balance.

The results from our study suggest that the regularity of the trunk accelerations of individuals with MS can be improved with a therapeutic exercise intervention. Moreover, this improvement in the regularity was related to improvements in walking endurance, cadence, and velocity. These results suggest that individuals with MS have a better ability to stabilize their trunk during walking following therapeutic interventions. Potentially, the therapeutic intervention employed in the current study promoted improvements in the motor control strategies of individuals with MS. It is possible that the therapeutic intervention promoted improvements in the strategies used by individuals with MS to compensate for the reduced somatosensory conduction typically seen in these individuals.[13] The improvements in such areas may have promoted better stability during walking and thus allowed for the adoption of a more normal gait pattern and improved walking endurance.

After completing the therapeutic exercise intervention, the participants had improvements in their mobility including better walking endurance and faster walking speed, which was accomplished by using a longer step length. In fact, after the intervention, the participants with MS were able to take similar step lengths as the healthy age-matched control. Our results are comparable to those in previous investigations which evaluated the influence of therapeutic programs such as combined exercise training, strength training, and yoga therapy.[53,54,104] Our current therapeutic intervention was unique from these previous interventions because it combined strength exercises, balance training, and treadmill walking into one session. Additionally, the frequency of sessions was much higher than what has previous been reported. The outcomes from our study suggest that intervention programs may not need to focus on one area of impairment such as balance, mobility, or strength. Rather potentially spending a short amount of time during a therapeutic session upon multiple areas problematic to an individual with MS may promote beneficial improvements in the mobility of individuals with MS. Moreover, our results suggest that completing more activity in short segments throughout the day may promote beneficial improvements in the mobility of individuals with MS. Future investigations should continue to interrogate the optimal dosage and type of therapeutic interventions for promoting improvements in the mobility of individuals with MS.

In conclusion, the outcomes from our study indicate that after six weeks of a therapeutic exercise program, individuals with MS exhibit improved walking speeds, step lengths, and walking endurance. Moreover, these individuals displayed more normal amounts of trunk acceleration variability and more regular trunk accelerations during walking, which were related to the improvements in walking speeds and endurance. Altogether, these results suggest that potentially the less regular trunk accelerations during walking may promote the adoption of compensatory strategies by individuals with MS.

DISCUSSION

Compensatory Gait Strategies

The first main purpose of this dissertation was to gain a more comprehensive understanding of the compensatory strategies adopted by individuals with MS to maintain mobility. Moreover, this main purpose sought to quantify potential factors contributing to the walking limitations of individuals with MS, thus promoting the adoption of these compensatory strategies. This dissertation specifically explored the influence that reduced functioning of the ankle musculature may have upon the gait strategies of individuals with MS. The first hypothesis explored was that individuals with MS would exhibit a reduction in the amount of positive mechanical work generated by the ankle and an increased production of positive mechanical work by the hip during walking. This redistribution pattern would suggest that individuals with MS adopt a hip strategy to compensate for the reduced functioning of the ankle musculature. The second hypothesis for this main purpose was that individuals with MS would have reduced ankle motor control and that this reduced motor control would be related to the altered gait parameters typically observed in individuals with MS. The outcomes from these explorations will provide insight about the mobility limitations of individuals with MS which will be useful for developing therapeutic paradigms that can better target the compensatory strategies adopted by these individuals.

In the many studies conducted for this dissertation, our subjects with MS walked at slower walking velocities and cadences with shorter step lengths than healthy age-matched adults. Additionally, our subjects with MS had a reduced maximal ankle moment at toe off during walking. These results are not surprising because they agree with the numerous investigations that have quantified the gait of individuals with MS in the past.[5,97,119] In fact the subjects that participated in our current studies exhibited even more reduced spatiotemporal kinematics than has previously been reported for individuals with MS suggesting that the subjects in the current studies had a higher amount of disability and potentially greater mobility limitations. We also observed that our individuals with MS had significantly weaker ankle musculature than healthy age-matched adults. This was not a surprising finding because it is well known that individuals with MS have vast reductions in muscle strength. Altogether these results suggest that our subjects with MS displayed similar alterations in their walking patterns and muscle strength as those that have previously been reported for individuals with MS.

Our hypothesis that individuals with MS would generate a reduced amount of positive mechanical work at the ankle but an increased amount of positive mechanical work at the hip during walking was supported by the outcomes of the study reported in Chapter 1. This indicates that individuals with MS may adopt a hip dominant strategy during walking to compensate for the reduced functioning of the ankle musculature. Potentially, this compensatory strategy is selected by individuals with MS because of the neuromuscular alterations typically seen at the ankle in these individuals. It has previously been suggested that spasticity, muscle weakness, or altered muscle recruitment patterns at the ankle contribute to the walking deficits in individuals with MS.[13,63,134,147] Therefore, any one of these alterations may have contributed to the reduced mechanical work generation at the ankle in individuals with MS. However, it is also possible that the reduced ability of the ankle to generate a normal amount of mechanical work is due to the decreased motor control of the ankle, which was measured in Chapter 2.

The results from Chapter 2 indicated that individuals with MS have an increased amount of error during a dynamic isometric motor task with their ankle plantarflexors. This suggests that individuals with MS have reduced motor control of the ankle musculature; potentially due to the neuromuscular alterations (i.e., spasticity) or as a result of the damage to the central nervous system caused by MS. We also did observe a relationship between the reductions in ankle motor control and muscle strength, which suggests that muscle weakness may contribute to the reduced ankle motor control. Moreover, it was found that the reduced motor control at the ankle was related to slower walking velocities, shorter step lengths, and lower maximal ankle joint moments generated during walking. These relationships suggest that the altered gait patterns of individuals with MS may not be solely due to decreased muscle strength or increased spasticity; rather, they may be due to decreased motor control of the ankle. Even though the relationship between the ankle motor control and the amount of positive mechanical work generated at the ankle and hip was not interrogated in the dissertation, it seems plausible that there would be a relationship between these variables. This relationship should be further explored in future investigations in order to fully understand how decreased motor control at the ankle may contribute to the compensatory strategies adopted by individuals with MS to maintain their mobility.

Therapeutic Interventions

This second main purpose of this dissertation sought to evaluate the influence of novel physical therapy protocols upon the balance and mobility of individuals with MS. This main purpose attempted to build upon the knowledge gained from the studies completed for the first two chapters. Specifically, the first hypothesis of this main purpose was that a novel therapeutic paradigm that focused upon the control of the ankle would not only promote clinically relevant improvements in the gait and posture of individuals with MS, but also promote significant improvements in ankle motor control. Moreover, it was hypothesized that the improvements in ankle motor control would be related to the improvements seen in the gait and posture of individuals with MS. The outcomes from these studies will build upon the knowledge gained from the first main purpose of the dissertation and will provide foundational information for the development of superior therapeutic treatment options for promoting improvements in the mobility of individuals with MS.

The first novel physical therapy intervention explored in this dissertation specifically focused on the ankle musculature and the acquisition of motor adaptation techniques for promoting better postural control and mobility. The outcomes from this investigation indicated that the walking speed and step lengths of individuals with MS were improved after the completion of the intervention and that postural balance was also significantly improved. More importantly there was a substantial improvement in the ankle motor control; this improvement was so substantial that there was no longer a difference in the motor control of the ankle between the individuals with MS and the healthy control group. To our knowledge this is the first investigation that has identified improved ankle motor control following a therapeutic intervention for individuals with MS. This improvement in motor control was related to the improvements in postural balance but not to the improvements in the mobility of individuals with MS. The lack of relationship between the improvements in ankle motor control and mobility was not expected, especially since the results from the study in Chapter 2 suggested that better ankle motor control is related to faster walking speeds and step lengths. Potentially the lack of findings in the therapeutic investigation was due to the selection of a continuous isometric motor task to measure ankle motor control rather than a dynamic motor task similar to the one that was employed in the investigation for Chapter 2. Previous investigations have cited that a continuous isometric motor task may not be an appropriate measure of motor control for interrogating its relationship with a functional motor task such as walking.[15,95,129] Therefore, this was a limitation in the therapeutic study and the influence of this therapeutic paradigm upon the motor control of the ankle and its relationship to mobility could not be fully understood. Future investigations should explore whether improvements in a dynamic motor task may be related to improvements in gait following similar therapeutic interventions.

This first therapeutic study was limited in its application because even though the improvements in gait and posture were similar to or higher than the outcomes of previous intervention studies,[57,69,104] it was unable to be determined if the outcomes were due to the novel therapeutic paradigm or novel therapeutic dosage. Therefore, the investigation reported in Chapter 4 sought to address this dilemma. This investigation compared the outcomes from the original novel therapeutic program to the outcomes from a cohort of individuals who participated in a more traditional exercise program conducted at the same high frequency level. It was hypothesized that the original novel therapeutic intervention would result in greater improvements in the balance and mobility of individuals with MS than the therapeutic exercise program. However, our results did not support this hypothesis because both groups displayed similar improvements in walking velocity, step lengths, walking endurance, and postural balance. These outcomes suggest that activity type may not be the most important parameter for promoting clinically relevant improvements in gait and posture. Rather the dosage level may also be a vital parameter for promoting clinically relevant improvements. Altogether these outcomes appear to challenge the traditional viewpoint that individuals with MS should not participate in high amounts of activity because no adverse effects were observed during either high-frequency therapeutic intervention. Potentially, individuals with MS should be encouraged to participate in more daily physical activity. Future investigations are still needed in this area because the optimal dosage level for promoting clinically relevant improvements cannot be determined from this study. It is likely that the dosage level does not need to be quite as high as the interventions employed in the current investigations.

Potentially individuals with MS may attain similar improvements when completing a therapeutic protocol once a day for five consecutive days each week. Moreover, it is possible that a shorter duration, such as two weeks, of therapeutic protocols completed at the same high frequency of the current therapeutic interventions followed by a lower dosage maintenance period may promote clinically relevant improvements. Future investigations should compare the outcomes from these high-frequency physical therapy interventions to programs completed at more traditional dosage levels (two to three sessions per week) in order to fully understand the influence that dosage may have upon the balance and mobility of individuals with MS.

This second therapeutic investigation was limited in its insight toward whether the motor control of the ankle musculature can be improved with physical therapy interventions because it did not directly quantify the ankle motor control at any time point. Therefore, we were unable to determine whether the activity focus of the physical therapy was an important parameter for promoting improvements in the ankle motor control. It is possible that the original novel therapeutic intervention promoted greater improvements in the ankle motor control of individuals with MS because it focused specifically on the control of the ankle. However, since both therapeutic paradigms significantly improved walking velocity and step length, both of which were seen to be related to ankle motor control in Chapter 2, it is possible that both therapeutic paradigms significantly improved ankle motor control. This seems feasible if ankle motor control is influenced by the muscle strength of the ankle plantarflexors because both paradigms may have promoted vast improvements in this muscle strength. However, once again, this cannot be determined because the second therapeutic investigation did not evaluate muscle strength at any time point. Therefore, based on these limitations of the second therapeutic intervention, our understanding about the influence of therapeutic interventions upon the ankle motor control is still limited and should be interrogated further in future investigations.

It was originally hypothesized that the high-frequency therapeutic exercise program employed in the dissertation would promote a more normal distribution of mechanical work across joints during walking. It was suggested that mechanical work would act as a dynamic measure of motor control during walking; thus, an increase in the amount of positive work generated by the ankle during walking would suggest that the ankle motor control had improved. However, the small sample size and moderate to severe disability levels of the subjects who participated in our studies hindered this exploration. Appendix B provides a brief report on the results of the mechanical work analysis that was conducted on the cohort of subjects who were able to provide evaluable data for the mechanical work analysis. This cohort consisted of individuals with MS who were able to walk independently without the use of an assistive device during the experimental procedures. There were no significant improvements for any mechanical work outcomes after the therapeutic intervention, which may imply that the motor control of the ankle was not improved after this protocol. However, we are cautionary with these conclusions because there were only eight subjects in this analysis. Additionally, it appears that these individuals may have adopted additional compensatory strategies to address an increase in the degree of instability from having to complete the three-dimensional motion capture procedures with no assistive devices. Thus, these results may be limited in their interpretation. Future investigations should be completed to better understand the influence of physical therapy upon the mechanical work generated by individuals with MS during walking. These future investigations should control for the disability level of the subjects in order to counter any additional compensatory strategies that may be adopted during the experimental procedures by individuals with higher disability levels.

The observation that the high-frequency therapeutic exercise program was able to improve the structure of trunk acceleration variability during walking is a novel finding and suggests that individuals with MS have highly adaptable control strategies during walking. The investigation completed in Chapter 5 found that individuals with MS have less regular trunk accelerations during walking than healthy adults but that after the completion of the six week exercise program, the subjects exhibited more regular trunk acceleration. To our knowledge this study is the first that has identified improved trunk acceleration variability following a physical therapy intervention. Although the trunk accelerations were still less regular than healthy age-matched adults after the therapeutic intervention, the improvements in the trunk accelerations were related to the improvements in walking velocity, cadence, and walking endurance. It is possible that the improved structure of the trunk acceleration promoted more normal gait patterns due to increased stability during walking. Additionally, these outcomes also appear to suggest that the compensatory strategies adopted by individuals with MS such as reduced walking velocity may be due to an increased amount of instability caused by the variability within the trunk accelerations during walking. The results from this study, along with the improvements in ankle motor control reported in Chapter 3, suggest that individuals with MS exhibit highly adaptable control strategies during gait. Moreover, these studies suggest that therapeutic interventions may be able to promote more normal control strategies. This improved motor control may promote clinically relevant improvements in the gait or posture of these individuals. Future investigations should continue to evaluate the influence of therapeutic intervention upon the control strategies of individuals with MS.

Limitations

The research studies in this dissertation were limited because each investigation had a small sample size for each cohort or group. Specifically, the therapeutic intervention studies were limited because of the small sample size. Potentially having more subjects in each group would have augmented the differences between the groups. Additionally, larger sample sizes may have produced more robust relationships between the ankle motor control and the mobility measures. Another major limitation of the dissertation was that we did not evaluate potential underlying factors contributing to mobility limitations. Specifically, the relationship between spasticity and the gait alterations of individuals with MS was not able to be evaluated due to the small sample sizes. Spasticity was measured in the cohort of subjects who completed the experimental procedures reported in Chapters 1 and 2. However, due to the small sample sizes, only a brief descriptive analysis was conducted. The outcomes from this analysis are reported in Appendix C. This analysis was limited because all but one subject had spasticity present and there were not enough subjects to separate them into groups based on the severity of spasticity. Therefore, these results are purely descriptive and cannot provide us with any significant interpretive value. Spasticity was not measured for any of the therapeutic studies; therefore it is unknown whether spasticity was decreased after the physical therapy programs. Future investigations should consider spasticity as a potential contributing factor to the decreased motor control at the ankle and mobility limitations of individuals with MS. Moreover, future investigations should also consider other potential contributing factors to decreased ankle motor control such as altered muscle activation patterns, reduced muscle strength, or alterations in the neural activity.

Conclusions

In conclusion, this dissertation built upon the current literature which suggests that the ankle plantarflexors are primary limiting factors of the mobility of individuals with MS. The outcomes of the studies identified that individuals with MS adopt a hip strategy to potentially compensate for the reduced functioning of the ankle musculature and that the alterations in gait patterns may be due to decreased ankle motor control. Additionally, the outcomes from this dissertation suggest that this decreased ankle motor control can be improved with therapeutic interventions which target the ankle musculature. However, the dissertation did not observe a relationship in this improved ankle motor control and gait kinematics following the therapeutic interventions. Finally, the dissertation discovered that two types of high-frequency physical therapy can promote improvements in the posture and mobility of individuals with MS. Altogether these results provide clinicians and researchers new information concerning the compensatory strategies employed by individuals with MS during walking. It also provides preliminary information about what parameters of therapeutic interventions may be vital to promoting clinically relevant improvements in the balance and mobility of these individuals.

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APPENDIX A: SUPPLEMENTARY MATERIAL FOR CHAPTER 3

Table 7: Supplementary Material: All results pre and post therapy for the MS group for all variables.

Subject	Sensory Organization Test		Coefficient of Variation (%)		Normalized Maximum Voluntary Torque (Nm/kg)		Preferred Velocity (m/s)		Preferred Step Width (m)		Preferred Step Length (m)		Preferred Cadence (Steps/min)		Fast-as-Possible Velocity (m/s)		Fast-as-Possible Step Width (m)		Fast-as-Possible Step Length (m)		Fast-as-Possible Cadence (Step/min)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	59	64	3.33	2.91	0.53	0.83	0.87	1.05	0.14	0.15	0.47	0.52	110.9	120.2	1.12	1.34	0.09	0.11	0.51	0.58	132.2	139.6
2	66	60	3.59	2.06	0.60	0.53	0.71	0.78	0.15	0.16	0.42	0.45	104.1	103.6	0.92	0.93	0.19	0.15	0.48	0.52	116.0	108.0
3	13	68	6.66	1.19	0.40	0.43	0.71	0.83	0.10	0.08	0.38	0.46	113.5	107.8	0.98	1.44	0.09	0.07	0.39	0.56	152.7	154.7
4	46	50	2.21	1.08	0.49	0.46	0.41	0.58	0.05	0.06	0.44	0.53	56.6	66.1	0.62	0.80	0.06	0.06	0.51	0.59	72.0	82.5
5	63	72	5.36	2.91	0.23	0.50	0.97	1.00	0.12	0.15	0.53	0.65	110.1	92.9	1.28	1.65	0.12	0.19	0.59	0.78	131.4	127.2
6	63	78	5.10	1.56	0.35	0.56	0.85	1.01	0.20	0.15	0.51	0.59	99.9	101.5	1.12	1.23	0.16	0.07	0.61	0.62	110.0	120.4
7	38	75	4.59	3.80	0.22	0.44	0.40	0.82	0.11	0.09	0.29	0.43	83.6	115.0	0.67	1.02	0.10	0.11	0.37	0.46	108.2	133.4
8	66	77	5.89	1.38	0.71	0.54	0.63	0.67	0.11	0.11	0.47	0.50	80.7	80.2	0.87	0.82	0.09	0.10	0.54	0.54	96.0	91.5
9	48	79	1.10	2.80	0.68	0.53	0.88	0.89	0.19	0.16	0.44	0.45	121.0	118.7	1.27	1.17	0.18	0.17	0.58	0.54	133.1	129.4
10	56	60	2.36	2.28	0.52	0.95	0.80	0.73	0.20	0.22	0.35	0.44	136.9	99.6	0.84	1.38	0.21	0.20	0.33	0.45	152.6	185.8
11	41	69	4.58	3.06	0.58	0.50	0.52	0.60	0.12	0.10	0.41	0.44	77.2	81.9	0.69	0.73	0.11	0.10	0.48	0.51	87.1	87.1
12	64	68	1.94	2.52	0.45	0.96	0.73	1.07	0.15	0.12	0.49	0.64	89.5	102.9	1.29	1.38	0.11	0.09	0.61	0.69	126.9	120.3
13	44	55	7.85	1.30	0.34	0.59	10.2	0.99	0.12	0.13	0.68	0.67	91.2	87.6	1.07	1.11	0.17	0.18	0.61	0.57	106.1	116.8
14	53	72	5.44	4.60	0.29	0.44	0.54	0.51	0.14	0.15	0.51	0.52	64.0	59.8	0.82	0.74	0.15	0.13	0.62	0.65	80.4	71.0
15	58	70	2.32	0.54	0.58	0.37	0.56	0.70	0.11	0.10	0.39	0.46	85.8	96.8	0.74	0.95	0.12	0.10	0.40	0.49	109.9	117.9
Average ± SEM	**51.9 ± 3.7**	**67.8 ± 2.2**	**4.15 ± 0.5**	**2.27 ± 0.3**	**0.46 ± 0.04**	**0.57 ± 0.05**	**0.71 ± 0.05**	**0.81 ± 0.05**	**0.13 ± 0.01**	**0.13 ± 0.01**	**0.45 ± 0.02**	**0.52 ± 0.02**	**95 ± 5.6**	**96 ± 4.6**	**0.95 ± 0.06**	**1.11 ± 0.07**	**0.13 ± 0.01**	**0.12 ± 0.01**	**0.51 ± 0.02**	**0.57 ± 0.02**	**114 ± 6.3**	**119 ± 7.6**

APPENDIX B: MECHANICAL WORK IS NOT CHANGED AFTER PHYSICAL THERAPY

Introduction

Since the neuromuscular impairments of the ankle have been cited as a primary limiting factor to the mobility of individuals with MS, the influence of therapeutic protocols upon the ankle functioning have previously been explored.[62,63,134,147] Specifically, a 6-week elliptical training program was found to promote improvements in the joint torque at the hip and joint power at the ankle during walking.[62] Moreover, these joint torques and powers normalized to those of a healthy control group. These results suggest that the increases in muscle strength or muscle activation, that more than likely occurred as a result of the elliptical training, promoted improvements in the control of the lower extremities during walking. Additionally, the investigation in Chapter 3 indicated that a high-frequency therapeutic protocol that focused on motor adaptation strategies promoted improvements in the motor control of the ankle plantarflexor musculature. Following this therapeutic program, the control was normalized to that of the healthy control group and the improved control at the ankle was related to improved postural balance, but not to improvements in spatiotemporal kinematics during gait. This potentially may have been due to the dissimilarity between an isometric motor task and the dynamic nature of the motor control during gait. Nevertheless, the results from these two previous investigations suggest that individuals with MS are able to adapt their control strategies at the ankle following therapeutic interventions.

Despite the positive influence of therapeutic interventions upon the control of the ankle musculature and the overall mobility of individuals with MS, it is still relatively unknown whether these types of interventions can promote improvements in the distribution of mechanical work during walking in the joints of individuals with MS. The outcomes of Chapter 1 indicate that individuals with MS generate a reduced amount of mechanical work at the ankle and an increased amount of work at the hip during walking. Potentially, the neuromuscular alterations of the ankle, such as increased muscle weakness or spasticity, may limit the ankle’s ability to generate a sufficient amount of positive mechanical work to assist with forward progression of the body during gait and maintenance of gait speed. By quantifying the mechanical work generation by the ankle, knee, and hip joints during gait before and after therapeutic interventions, we may gain a better understanding about the motor control changes that occur during walking which may underlie the improvements in mobility that have been observed. The outcomes from this investigation may provide us information that will allow for better development of therapeutic protocols targeting the compensatory strategies employed by individuals with MS for maintaining gait speed.

Therefore, the purpose of this investigation was to evaluate the changes in the production of mechanical work at the ankle, knee, and hip joint during the stance phase of gait in our cohort of individuals with MS who completed the high-frequency therapeutic exercise cohort (TEC) program outlined in Chapter 4. We hypothesized that since there were significant improvements in walking velocity and step lengths after the TEC program, there would also be an improvement in the generation of positive net mechanical work at the ankle and a decrease in the amount of positive net mechanical work produced at the hip.

Methods

The 13 individuals who completed the TEC program in Chapter 4 (Mean Age: 54.8 ± 9 years, 7 female; EDSS = 5.3 ± 0.2; for full subject characteristics see Table 5 on page 62) also completed a three-dimensional gait analysis before and after completing the program. Procedures for the gait analysis are covered in Chapter 1 on pages 16-

17. In brief, subjects were outfitted with reflective markers placed bilaterally upon the lower extremities and then proceeded to walk at a self-selected pace along a 16-meter walkway which was instrumented with four force platforms (1200 Hz; Advanced Mechanical Technology, Inc., Watertown, MA, USA). The reflective markers were tracked by an eight-camera three-dimensional motion capture system (120 Hz; Vicon Motion Systems Ltd., Centennial, CO, USA). All subjects completed a sufficient number of walking trials in order to acquire at least three trials with consecutive foot contacts where each foot was positioned completely within the boundaries of separate force plates. Subjects were required to walk independently without the use of an assistive device such as a cane or walker; however, if a subject utilized an ankle-foot orthosis or special footwear for daily ambulation, they completed all trials with such devices in place. Subjects were allowed to rest as needed in between each walking trial so as to not become fatigued during experimental procedures.

All data was analyzed the same way as the procedures reported in Chapter 1, which are outlined on pages 16-17. The spatiotemporal kinematic variables of interest included velocity (meters/second), step length (meters), step width (meters), and cadence (steps/minute). The mechanical work variables of interest were the net mechanical work generated during the stance phase of gait at the ankle, knee, and hip joints. These mechanical work variables were found for both the more and less impaired legs of the subjects.

Therapeutic Protocol

The procedures for the TEC program are outlined on pages 58-59 in Chapter 4.

Statistical Analysis

Paired t tests were used to determine the differences in the spatiotemporal kinematics between the two time points (Pre/Post Therapy). Separate 2 x 3 repeated measures ANOVAs (Time x Joint) were used to interrogate the differences in the mechanical work at the ankle, knee, and hip joints before and after the therapeutic intervention for each leg. Post-hoc analyses were performed if necessary. An alpha level of 0.05 was used to interrogate all data for significance. The data is reported as the mean ± standard error of the mean.

Results

Even though all 13 subjects in the TEC completed the gait analysis procedures, only eight subjects were able to achieve the requirement of having consecutive foot contacts where each foot was positioned completely within the boundaries of separate plates, thus having evaluable data. Therefore, the reported outcomes are from the analyses performed on the data from eight subjects (Mean Age: 49.4 ± 2.8 years; 4 Female; EDSS: 5.1 ± 1.1; See Table 8 for additional subject characteristics).

Table 8: Baseline Subject Characteristics

Subject	Gender	Age (Years)	Diagnosis	Years with MS	EDSS	Assistive Device
1	M	48	SP	12	5.5	None
2	F	57	RR	12	4.0	None
3	F	36	SP	14	6.5	Walker
4	M	55	SP	4	4.5	None
5	M	59	RR	5	6.0	Carbonfiber AFO*
6	F	50	RR	15	4.5	None
7	F	50	RR	12	3.5	None
8[†]	M	40	RR	8	6.0	AFO
Average		49.4 ± 2.8		10.3 ± 1.4	5.1 ± 1.1	

* Was used during the walking trials

[†] Wore shoes during the walking trials

Spatiotemporal Kinematics

There were no significant differences in the walking velocity (Pre: 0.98 ± 0.05 m/s; Post: 1.02 ± 0.06 m/s; p = 0.24), step length (Pre: 0.53 ± 0.02 m; Post: 0.55 ± 0.02

m; p = 0.12), step width (Pre: 0.13 ± 0.01 m; Post: 0.15 ± 0.01 m; p = 0.12), or cadence (Pre: 107.5 ± 4 steps/min; Post: 106.7 ± 5 steps/min; p = 0.74) following the TEC program.

Mechanical Work More Impaired Leg

The repeated measures ANOVA for the more impaired leg did not find any significant Joint main effect (Ankle: -0.043 ± 0.03 J/kg; Knee: -0.032 ± 0.02 J/kg; Hip: 0.050 ± 0.04 J/kg; p = 0.10), Joint by Time interaction (p = 0.997; See Table 9), or Time main effect (Pre: -0.003 ± 0.03 J/kg; Post: -0.013 ± 0.02 J/kg; p = 0.783).

Mechanical Work Less Impaired Leg

The repeated measures ANOVA for the less impaired leg did not find any significant Joint main effect (Ankle: 0.035 ± 0.02 J/kg; Knee: -0.013 ± 0.01 J/kg; Hip: 0.072 ± 0.04 J/kg; p = 0.199), Joint by Time interaction (p = 0.350; See Table 2), or Time main effect (Pre: 0.015 ± 0.02 J/kg; Post: 0.048 ± 0.03 J/kg; p = 0.226).

Table 9: Net Mechanical Work at Each Joint for Each Leg

Time	**More Impaired Leg**			**Less Impaired Leg**		
	Ankle	**Knee**	**Hip**	**Ankle**	**Knee**	**Hip**
Pre	-0.04 ± 0.04	-0.02 ± 0.03	0.05 ± 0.06	0.02 ± 0.03	0.01 ± 0.01	0.02 ± 0.07
Post	-0.05 ± 0.04	-0.04 ± 0.02	0.05 ± 0.05	0.05 ± 0.03	-0.03 ± 0.02	0.12 ± 0.05

Discussion

The results of our initial exploration indicated that individuals with MS who completed a high-frequency TEC protocol significantly increased their walking velocity and step length. Therefore, this exploration sought to determine whether or not the mechanical work generated by the ankle, knee, and hip joint also improved following the high-frequency TEC protocol. We hypothesized that there would be a significant increase in the positive mechanical work generation by the ankle and decrease in positive mechanical work generation by the hip. However, our results did not display that the mechanical work at any joint significantly changed following the TEC protocol. Additionally, in the current subset of subjects, there were no significant improvements in the spatiotemporal kinematics of walking.

A previous investigation has found that a six week elliptical training program for individuals with MS significantly improved the joint torque generation at the hip and joint power generation at the ankle.[62] Specifically, the torque at the hip and power at the ankle normalized to those of the healthy control group. These results suggest that after the elliptical training, the individuals with MS were able to adopt new and more normal strategies for maintaining their mobility. We expected to see similar outcomes in the mechanical work generation following our therapeutic program since we had initially observed improvements in step length and walking velocity in our entire TEC. Joint torques and powers are directly related to walking velocity; specifically, as an individual increases his/her walking velocity, the joint torques and powers also increase.[19,84,92,153,154] The outcomes from our study potentially indicate that our subjects were unable to adapt their mechanical work production to generate an increased amount of mechanical work at the ankle. Spasticity and muscle weakness at the ankle are two of the neuromuscular impairments that are typically cited as primary contributors to the mobility limitations of individuals with MS.[63,134,147] It is possible that the TEC protocol did not significantly improve the spasticity and/or weakness at the ankle in our subjects; thus limiting the improvements in mechanical work production at the ankle.

It is possible that we did not see a significant improvement in the mechanical work production by subjects in the TEC because our sample size was relatively small. Out of 13 participants in our original investigation, only 8 were able to complete the experimental procedures and have evaluable data for investigating mechanical work. This resulting sample size was 1/3 of the sample size of a previous investigation exploring the influence of a therapeutic exercise program upon the joint power and torque generation in individuals with MS;[62] therefore, potentially the sample size was not large enough to detect any improvements following the therapeutic protocol. Future investigations using larger sample sizes should continue to interrogate whether mechanical work generation can be improved following a high-frequency TEC protocol.

Surprisingly, we also found no improvements in the spatiotemporal kinematics of gait in this current investigation, which was unexpected because the subjects who completed these experimental procedures were part of our initial investigation, which reported improved step lengths and walking velocities after the TEC protocol. Potentially, our lack of findings in this investigation is due to the difference in methodology used to quantify the spatiotemporal kinematics of gait between the two investigations. The spatiotemporal kinematics found in Chapter 4 for our initial exploration were quantified using a digital mat (GAITRite®, CIR Systems Inc., Sparta, NJ) which measures footfall data through pressure sensors embedded in the mat. This method of quantifying the spatiotemporal kinematics is relatively simple and the subjects were allowed to utilize the assistive devices (i.e., cane or wheeled walker) which they would typically use on a regular basis for community ambulation. Conversely, the motion analysis methodology used in the current investigation required that subjects completed the walking trials independently without the use of such assistive devices. Even though previous investigations have found a high degree of similarity between these methodologies for quantifying gait parameters,[148] it is possible that our subjects adopted different walking strategies for the different methodologies. Analysis of the digital mat data for our subset of 8 subjects revealed that these subjects did significantly improve their velocity (Pre: 0.88 ± 0.07 m/s; Post: 0.99 ± 0.04 m/s; $p = 0.05$) and step length (Pre: 0.53 ± 0.02 m; Post: 0.58 ± 0.02 m; $p = 0.02$) following the TEC program when allowed to utilize their regular assistive devices. It is possible that the subjects did not display improved spatiotemporal kinematics in the current study because they employed additional compensatory techniques to address the increased instability they faced by not being able to rely upon an assistive device for additional support. This would also potentially influence the mechanical work being generated by the lower extremity joints during walking. Therefore, potentially different control strategies were employed when completing each type of gait analysis between the two studies.

In conclusion, the TEC program did not appear to improve the mechanical work generation by any of the joints on either leg of individuals with MS. Due to the many limitations in this current study, we are cautionary with these concluding remarks and are hopeful that future studies with larger sample sizes may better identify the influence of the TEC program upon the mechanical work production of the lower extremities, especially the ankle.

APPENDIX C: DESCRIPTIVE ANALYSIS OF THE RELATIONSHIP BETWEEN SPASTICITY AND GAIT IN INDIVIDUALS WITH MULTIPLE SCLEROSIS

Introduction

Spasticity can be defined as a velocity-dependent increase in tonic stretch reflexes and exaggerated tendon reflexes resulting from increased excitability of the stretch reflex.[91] Individuals with multiple sclerosis (MS) often exhibit signs of spasticity, especially in the lower extremities. In fact, more than 80% of all individuals with MS exhibit some level of spasticity.[123] Spasticity of the ankle musculature, along with muscle weakness, has been cited as a potential limiting factor to the balance and mobility of individuals with MS. However, previous investigations have produced conflicting results as to whether or not spasticity influences the mobility of individuals with MS.

Sosnoff et al.[134] found that individuals with MS who had spasticity had a slower timed 25-foot walk, a slower Timed Up and Go time, walked shorter distances during the 6-minute walk test, and had a higher score on the Multiple Sclerosis Walking Scale-12 than individuals with MS who did not have spasticity. These outcomes are supported by an investigation that explored whether a higher self-perceived impact of spasticity was related to the altered spatiotemporal kinematics seen in the gait of individuals with MS.[4] This study discovered that a higher self-perceived impact of spasticity was associated with decreases in cadence and velocity along with an increase in step time and base of support. However, Wagner et al.[147] found little association between spasticity and the same mobility measures used in Sosnoff et al.'s[134] investigation. Additionally, Wagner et al.[147] did not find any association between muscle strength and spasticity.

Therefore, the relationship between spasticity and the mobility deficits of individuals with MS is still not well understood. By exploring and quantifying this relationship, we may gain a better understanding about the underlying factors contributing to the gait deficits and compensatory strategies employed by individuals with MS. This information may allow for therapeutic interventions to be able to better target these underlying causes, thus promoting improvements in mobility. The objective of this analysis was to explore whether the mobility deficits and compensatory strategies that were measured in Chapters 1 and 2 may be influenced by the presence of spasticity in the ankle plantar-flexors on the more impaired leg of our subjects with MS.

Methods

The same cohort of individuals with MS that were used for Chapters 1 and 2 were used for this analysis (Mean Age: 53.1 ± 7.6; 10 female; for all subject characteristics see Table 1 on page 18 in Chapter 1 or Table 2 on page 27 in Chapter 2).

Spasticity Measure

The lower extremity portions of the modified Ashworth scale (MAS) were utilized to evaluate the presence and severity of spasticity in the legs of all subjects. A licensed physical therapist (RH) conducted the MAS on all subjects. Scores on the MAS range from 0 to 4; a score of 0 indicates there is no increase in muscle tone and a score of 4 indicates that the affected part is rigid. The maximum MAS score for the plantarflexor (PF) musculature of the most impaired leg was selected for use in the final analyses.

Gait Measures

The spatiotemporal gait kinematics, maximum moment generated by the ankle during walking, and the mechanical work at the ankle, knee, and hip joint during the stance phase of walking were quantified using the three-dimensional motion analysis procedures and data analyses methods outlined in Chapters 1 and 2.

Dynamic Isometric Ankle Force Control & Strength

Dynamic isometric control of the ankle plantarflexors was interrogated using the plantarflexion task outlined on pages 28-30 in Chapter 2. Also, muscle strength was quantified using the maximal isometric voluntary torque (MVT) procedures reported in the same chapter.

Statistical Analyses

Due to the small sample size, no statistical analyses were performed to interrogate the potential relationship between the spasticity at the ankle and the gait and motor control variables. After initial exploration of the data, it was clear that all but one of the subjects had some level of spasticity in their ankle musculature on their most impaired leg. Therefore, allocating the subjects into two groups based on whether or not spasticity was present, as has been used in previous investigations, was not an option.[134,147] Further inspection of the data displayed that there were spasticity scores that only had one subject in them, thus preventing us from calculating average results for subjects with each level of spasticity. Therefore, the results reported here are descriptive in nature and cannot provide a definitive conclusion about the relationship between spasticity and the mobility deficits of individuals with MS. Future investigations utilizing a larger sample size with more subjects in each MAS PF score should be conducted to better evaluate if spasticity significantly impacts these mobility measures.

Results and Discussion

The complete results for the MAS scores, gait variables, ankle motor control variables, and MVT for the most impaired leg can be found in Tables 10 and 11.

Modified Ashworth Scale Scores

All but one subject had spasticity present in at least one muscle measured and had bilateral spasticity. The highest MAS score in all muscle groups for the most impaired leg was present in either the gastrocnemius and/or the soleus for 12 out of the 14 subjects. One of the subjects who did not have the most significant spasticity present in their ankle musculature exhibited the highest amount of spasticity in their hamstrings and the other subject exhibited it in their quadriceps. The most frequently occurring MAS PF score was 1+ suggesting that the majority of the subjects (seven subjects) had a slight increase in tone in their plantarflexors. The second most frequently occurring MAS PF score was 2 with four subjects displaying this score. The MAS PF scores of 0, 1, and 3 had one subject each and there were no subjects with a MAS PF score of 4.

Table 10: Results for the MAS Scores and Spatiotemporal Kinematics

Subject	MAS Hams.	MAS Quads.	MAS Gastroc.	Soleus	Velocity (m/s)	Step Width (m)	Step Length (m)	Cadence (steps/min)
1	0	1+	2	1+	0.92	0.13	0.58	90.1
2	1	1	2	2	0.92	0.19	0.52	102.9
3	0	0	1+	1+	1.01	0.12	0.54	106.1
4	0	0	1+	1+	0.97	0.13	0.30	127.1
5	1	1+	3	3	0.87	0.17	0.55	87.8
6	1	0	2	1	0.91	0.22	0.48	109.7
7	1+	1	1	0	0.78	0.15	0.47	106.0
8	0	0	1+	1	0.97	0.24	0.45	112.5
9	1+	1+	2	1	1.01	0.13	0.47	118.8
10	0	1	1+	1+	0.99	0.20	0.48	110.4
11	0	0	0	0	1.06	0.23	0.55	114.9
12	0	0	1+	1	1.06	0.15	0.60	102.9
13	2	3	1+	1	0.89	0.23	0.47	97.4
14	0	0	0	1+	0.92	0.16	0.52	93.9

Abbreviations: MAS – modified Ashworth Scale; Hams – hamstrings; Quads – quadriceps; Gastroc – gastrocnemius.

Velocity

The velocity results for all MAS PF scores are displayed in Figure 13A. The average velocity for the all subjects was 0.97 ± 0.02 m/s. The fastest velocity being produced by the subject with no reported spasticity (1.06 m/s) and the slowest velocity being produced by the subject with the MAS PF score of 1 (0.78 m/s). The subject with the highest measured PF spasticity (MAS PF score of 3) produced the second slowest velocity (0.87 m/s). The individuals with a MAS PF score of 1+ walked at an average velocity of 0.97 ± 0.02 m/s and the individuals with a MAS PF score of 2 walked at an average velocity of 0.94 ± 0.02 m/s. With the exception of the subject with the MAS PF of 1, it appears that there may be a trend that as the MAS PF score increases (i.e. spasticity increases), walking velocity decreases.

Step Length

The step length results for all MAS PF scores are displayed in Figure 13B. The average step length for all the subjects was 0.50 ± 0.04 m. The longest and shortest step lengths produced by individuals with a MAS PF score of 1+ (Longest: 0.60 m; Shortest: 0.30 m). The average step length for the individuals with a MAS PF score of 1+ was 0.48 ± 0.04 m. The average step length for the individuals with a MAS PF score of 2 was 0.51 ± 0.02 m. The individual with the MAS PF score of 1 had a step length of 0.47 m and the individuals with the MAS PF scores of 0 and 3 both had a step length of 0.55 m. Based on these results, it is hard to determine whether spasticity may influence step lengths. Especially since the individual with no measured spasticity walked with the same step length as the individual with the highest measured ankle spasticity. Moreover, the individuals with slight spasticity (MAS PF scores of 1 or 1+) on average took shorter step lengths than the individuals with more marked increased in tone (MAS PF score of 2).

Step Width

The step width results for all MAS PF scores are displayed in Figure 13C. The average step width for all the subjects was 0.18 ± 0.01 m. The widest step width was produced by the subject with a MAS PF score of 0 (0.23 m) and the most narrow step width was produced by a subject with a MAS PF score of 1+ (0.12 m). The average step width for the subjects with a MAS PF score of 1+ was 0.18 ± 0.02 m and the average step width for the subjects with a MAS PF score of 2 was 0.17 ± 0.02 m. The subject with the MAS PF score of 1 walked with a step width of 0.15 m and the subject with the MAS PF score of 3 walked with a step width of 0.17 m. Based on these results, it does not appear that spasticity influences step width. This interpretation is based upon the fact that even though the individuals with slight spasticity (MAS PF score of 1+) or no spasticity had wider steps than the subjects with more marked spasticity (MAS PF scores of 2 or 3), the individual with a MAS PF score of 1 had a more narrow step width than any of these groups, and an individual with a MAS PF score of 1+ produced the most narrow step length.

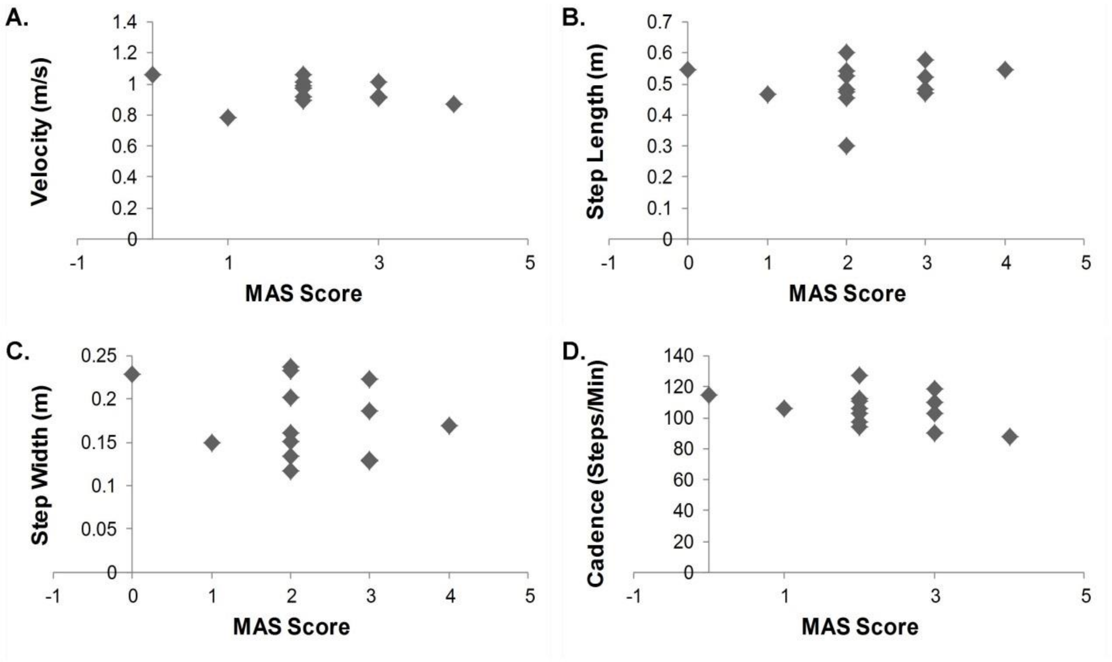

Figure 13: Spatiotemporal Kinematics Results by MAS PF Scores. A) The walking velocity results by MAS PF scores. **B)** The step length results by MAS PF scores. **C)** The step width results by MAS PF scores. **D)** The cadence results by MAS PF scores. For the scatter plots, the MAS PF scores have been converted to the following numerical scores: 0 = 0, 1 = 1, 1+ = 2, 2 = 3, 3 = 4, 4 = 5.

Cadence

The cadence results for all MAS PF scores are displayed in Figure 13D. The average cadence for all subjects was 105.8 ± 3.0 steps/min. The fastest cadence was 127.1 steps/min and was produced by an individual with a MAS PF score of 1+ and the slowest cadence was 87.8 steps/min produced by the individual with a MAS PF score of 3. The average cadence for the subjects with a MAS PF score of 1+ was 107.2 ± 4.2 steps/min and the average cadence for the subjects with a MAS PF score of 2 was 105.4 ± 6.0 steps/min. The individual with a MAS PF score of 1 walked with a cadence of 106.0 steps/min and the subject with no measured spasticity walked with a cadence of 114.9 steps/min. With the exception of the individual who walked at the fastest cadence, it appears that spasticity may influence cadence because the average cadences decreased between the MAS PF scores of 1+ and 2. Additionally, the individual with the highest measured spasticity walked with the slowest cadence. Therefore, it is possible that a person with a higher amount of spasticity at the ankle may walk with a slower cadence.

Table 11: Results for the Maximal Ankle Moment, Mechanical Work, MVT, and Ankle Control Measures

Subject	Max. Moment (Nm/kg)	Ankle Mech. Work (J/kg)	Knee Mech. Work (J/kg)	Hip Mech. Work (J/kg)	Isometric MVT (Nm/kg)	RMS Fast	RMS Slow
1	1.30	0.02	-0.03	-0.01	0.70	0.16	0.07
2	1.46	-0.05	-0.03	0.18	0.52	0.15	0.20
3	0.16	0.15	-0.03	-0.07	0.20	0.19	0.17
4	0.99	0.04	0.04	-0.26	0.30	0.13	0.07
5	1.02	0.01	0.03	0.05	0.17	0.14	0.08
6	1.35	-0.04	-0.01	-0.07	0.68	0.10	0.09
7	1.31	0.03	-0.07	0.20	0.73	0.15	0.12
8	1.06	-0.10	0.02	0.05	0.28	0.18	0.10
9	1.00	0.05	-0.06	-0.24	0.14	0.17	0.09
10	0.94	0.09	-0.02	-0.13	0.47	0.17	0.14
11	1.18	0.04	-0.03	0.15	0.33	0.12	0.09
12	1.56	0.03	-0.01	0.19	0.53	0.10	0.09
13	1.17	-0.05	-0.01	0.01	0.64	0.10	0.09
14	0.96	-0.10	-0.18	-0.02	0.28	0.10	0.08

Abbreviations: Mech – mechanical; MVT – maximal voluntary torque; RMS – root mean square.

Maximal Ankle Moment during Gait

The maximal ankle moment results for all MAS PF scores are displayed in Figure 14A. The average maximal ankle moment during gait for all subjects was 1.10 ± 0.30 Nm/kg. The highest and lowest maximal ankle moment was produced by individuals with a MAS PF score of 1+ (Highest: 1.56 Nm/kg; Lowest: 0.16 Nm/kg). The average maximal ankle moment during gait generated by individuals with a MAS PF score of 1+ was 0.98 ± 0.16 Nm/kg and the average maximal ankle moment during gait generated by individuals with a MAS PF score of 2 was 1.28 ± 0.10 Nm/kg. The subject with a MAS PF score of 0 generated a maximal ankle moment of 1.18 Nm/kg and the subjects with MAS PF scores of 1 and 3 generated ankle moments of 1.31 Nm/kg and 1.02 Nm/kg respectively. These results suggest that there may not be a relationship between the maximal torque generated by the ankle during gait and the spasticity at the ankle. This is because the subjects who had more marked levels of spasticity (MAS PF score of 2) generated a stronger moment at the ankle during walking than those with less of an increase in tone (MAS PF score of 1+). Three out of the four subjects with a MAS PF score of 2 were among the top five subjects in terms of maximal ankle moment generated during walking while four of the seven subjects with a MAS PF score of 1+ were among the bottom four subjects in terms of maximal ankle moment generated during walking. Moreover, both the subject with no reported spasticity and the subject with the highest level of measured spasticity were grouped in the middle of the entire group in terms of maximal ankle moment generated during walking. Therefore, based on this data, it appears that ankle spasticity may not influence the maximal ankle moment generated during walking.

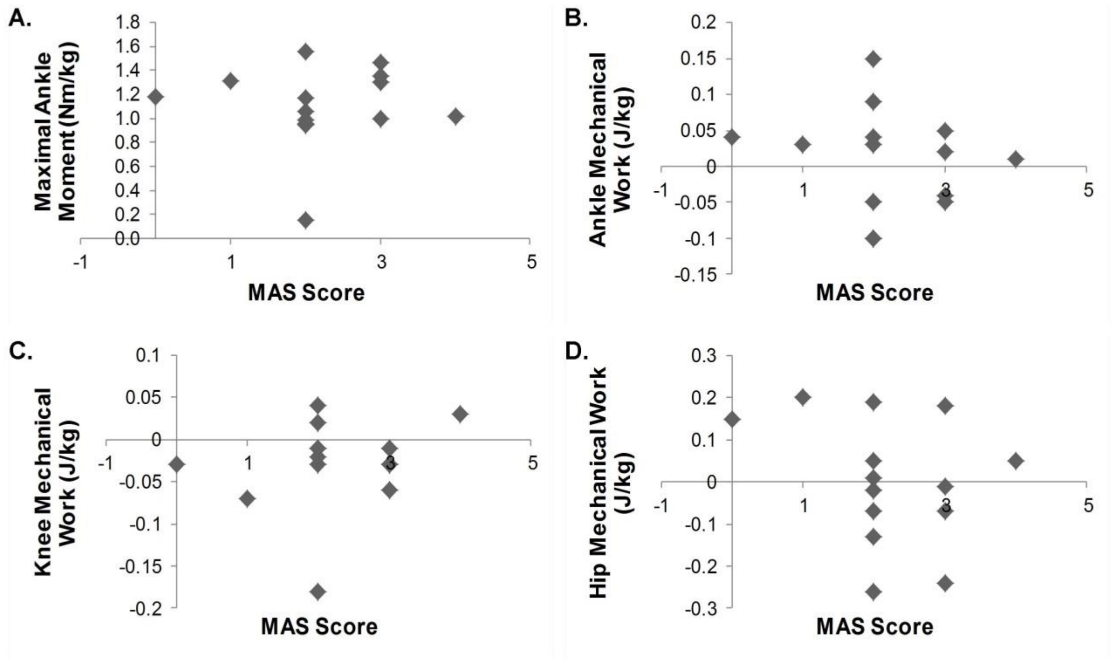

Figure 14: Maximal Ankle Moment and Mechanical Work Results by MAS PF Scores. A) The maximal ankle moment during walking results by MAS PF scores. **B)** The ankle mechanical work during walking results by MAS PF scores. **C)** The knee mechanical work during walking results by MAS PF scores. **D)** The hip mechanical work during walking results by MAS PF scores. For the scatter plots, the MAS PF scores have been converted to the following numerical scores: 0 = 0, 1 = 1, 1+ = 2, 2 = 3, 3 = 4, 4 = 5.

Mechanical Work

The ankle mechanical work results for all MAS PF scores are displayed in Figure 14B. The average positive mechanical work produced by the ankle of the entire group was 0.009 ± 0.02 J/kg. The subjects who produced the most and least positive mechanical work at the ankle had a MAS PF score of 1+ (Most: 0.15 J/kg; Least: -0.1 J/kg). The average positive mechanical work generated by the ankle of the individuals with a MAS PF score of 1+ was 0.009 ± 0.04 J/kg and the average generated by the ankle of the individuals with a MAS PF score of 2 was -0.005 ± 0.02 J/kg. The subject with no measured spasticity generated a positive mechanical net work at the ankle of 0.04 J/kg while the subjects with the MAS PF scores of 1 and 3 generated 0.03 and 0.01 J/kg net mechanical work at the ankle. Based on this data, it does not appear that spasticity influences the mechanical work generated at the ankle.

The knee mechanical work results for all MAS PF scores are displayed in Figure 14C.The average net mechanical work at the knee for the entire group was -0.027 ± 0.03 J/kg. The most and least mechanical work generated at the knee was produced by individuals with a MAS PF score of 1+ (Most: 0.04 J/kg; Least: -0.18 J/kg). The average mechanical work generated at the knee by individuals with a MAS PF score of 1+ was -0.027 ± 0.03 J/kg and the average mechanical work generated at the knee by individuals with a MAS PF score of 2 was -0.033 ± 0.01 J/kg. The mechanical work generated the knee by the individuals with MAS PF scores of 0, 1, and 3 were -0.03, -0.07, and 0.03 J/kg respectively. These results suggest that spasticity at the ankle may not influence the mechanical work generated by the knee during gait. The subjects with MAS PF scores of 0, 1+, and 2 are within 0.006 points of each other suggesting that these subjects generate relatively the same amount of negative mechanical work at the knee. Additionally, the subject with a MAS PF score of 1 generate the most negative net mechanical work and the subject with a MAS PF score of 3 actually generated a positive net mechanical work. Therefore, a relationship between spasticity and net mechanical work at the knee is difficult to see.

The hip mechanical work results for all MAS PF scores are displayed in Figure 14D.The average net mechanical work produced at the hip for the entire group was 0.002 ± 0.04 J/kg. The highest amount of positive net mechanical work at the hip was generated by the individual with the MAS PF score of 1 (0.2 J/kg) and the lowest amount of positive net mechanical work at the hip was generated by an individual with a MAS PF score of 1+ (-0.26 J/kg). The average net mechanical work produced at the hip for the individuals with a MAS PF score of 1+ was -0.033 ± 0.05 J/kg and the average net mechanical work produced at the hip for the individuals with a MAS PF score of 2 was -0.035 ± 0.09 J/kg. The individuals with the MAS PF scores of 0 and 3 produced mechanical work of 0.15 and 0.05 J/kg respectively at the hip. These outcomes do not appear to suggest that spasticity influences the net mechanical work generated at the hip. This outcome was drawn based on that the subject with only a slight increase in tone (MAS PF score of 1) had a greater amount of positive mechanical work generated by the hip than the individual with no measured spasticity. Moreover, the subject with a considerable amount of spasticity (MAS PF score of 3) had a positive net mechanical work while subjects with less spasticity (MAS PF scores of 1+ and 2) generated a negative net mechanical work. This negative get mechanical work was also relatively the same between the individuals with MAS PF scores of 1+ and 2. Therefore, it is difficult to determine whether there is an influence of spasticity upon the net mechanical work generated at the hip during walking.

Maximal Isometric Voluntary Torque

The MVT results for all MAS PF scores are displayed in Figure 15A.The average MVT produced by all subjects was 0.43 ± 0.06 Nm/kg. The highest MVT, implying the strongest subject, was produced by the individual with a MAS PF score of 1 (0.73 Nm/kg) while the lowest MVT, implying the weakest subject, was produced by a subject with a MAS PF score of 2 (0.14 Nm/kg). The subject with the highest measured spasticity in the ankle (MAS PF score of 3) produced the second lowest MVT (0.17 Nm/kg). The average MVT for the subjects with a MAS PF score of 1+ was 0.39 ± 0.06 Nm/kg and the average MVT for the subjects with a MAS PF score of 2 was 0.51 ± 0.13 Nm/kg. The subject who had no measured spasticity at the ankle (MAS PF score of 0) had a MVT of 0.33 Nm/kg. Based on these outcomes, it does not appear that spasticity has any influence on the MVT, which suggests that it does not affect the muscle strength of the ankle plantarflexor muscles. This conclusion was drawn because the individuals with more marked increase in tone (MAS PF score of 2) had higher MVTs than the individuals with less increases in muscle tone (MAS PF of 1 or 1+). Additionally, the individual with no measured spasticity at the ankle had a lower MVT than the average of all the subjects. Therefore, it is difficult to identify a trend in the data to determine whether spasticity influences muscle strength at the ankle.

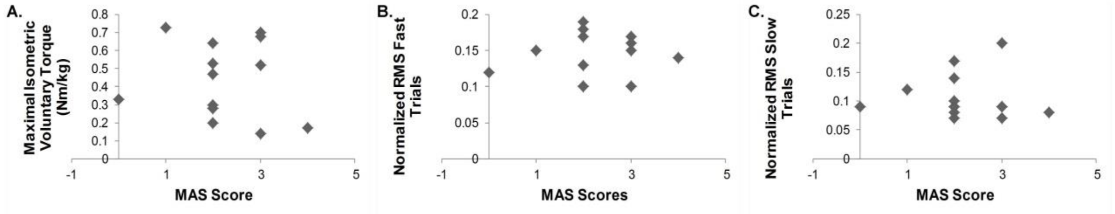

Figure 15: Maximal Voluntary Torque, and Root Mean Square Results Separated by MAS PF Scores. A) The maximal voluntary torque results separated by MAS PF scores. **B)** The RMS results for the Fast Trials separated by MAS PF scores. **C)** The RMS results for the Slow Trials separated by MAS PF scores. For the scatter plots, the MAS PF scores have been converted to the following numerical scores: 0 = 0, 1 = 1, 1+ = 2, 2 = 3, 3 = 4, 4 = 5.

Dynamic Isometric Ankle Force Control

The RMS for the Fast Trials results for all MAS PF scores are displayed in Figure 15B.The average RMS for the Fast Trials for all subjects was 0.14 ± 0.01. Individuals with a MAS PF score of 1+ had the highest (most error) and lowest (least error) RMS for the Fast Trials (Highest: 0.19; Lowest: 0.10). The average RMS during the Fast Trials for the individuals with a MAS PF score of 1+ was 0.14 ± 0.02 and the average RMS during the Fast Trials for the individuals with a MAS PF score of 2 was 0.15 ± 0.02. The individual with a MAS PF score of 0 had a RMS of 0.12 during the Fast Trials while the individuals with MAS PF scores of 1 and 3 had a RMS of 0.15 and 0.14 respectively during the Fast Trials. These results suggest that spasticity does not influence the motor control during the Fast Trials of a dynamic isometric motor task. Even though the individual with no measured spasticity had the lowest amount of error in their force generation, it was within 0.03 of the average of the group with a marked increase in tone. Moreover, the individuals with spasticity present (MAS PF scores ≥ 1) all produced relatively the same amount of error in the force generation at the ankle during the Fast Trials.

The RMS for the Slow Trials results for all MAS PF scores are displayed in Figure 15C.The average RMS for the Slow Trials for all subjects was 0.11 ± 0.01. The lowest RMS (least error) for the Slow Trials was produced by both a subject with a MAS PF score of 1+ and a subject with a MAS PF score of 2 (0.07), while the highest RMS (most error) was produced by a subject with a MAS PF score of 2 (0.2). The average RMS for the Slow Trials of the subjects with a MAS PF score of 1+ was 0.11 ± 0.01 and the average RMS for the Slow Trials of the subjects with a MAS PF score of 2 was 0.11 ± 0.03. The individuals with MAS PF scores of 0, 1, and 3 had a RMS for the Slow Trials of 0.09, 0.12, and 0.08 respectively. These results suggest that spasticity may not influence the motor control at the ankle during Slow Trials of a dynamic isometric force generation task. This conclusion as based on the recognition that the average amount of error produced by the subjects with slight increases in tone (MAS PF score of 1+) was the same as that of the subjects with more marked increase in tone (MAS PF score of 2). Additionally, the individual with considerable increases in tone at the ankle (MAS PF score of 3) had less error in their force generation than the individual with no measured spasticity. Therefore, it appears that spasticity may not influence the motor control at the ankle during a dynamic isometric motor task.

Conclusions

The purpose of this investigation was to explore whether spasticity potentially influenced the gait alterations and changes in motor control of the ankle seen in our subjects with MS in Chapters 1 and 2. All but one of our subjects displayed PF spasticity with the majority of the sample having a slight increase in tone. Due to the small sample size and limited distribution within the MAS PF scores, only a descriptive analysis was able to be completed. This descriptive analysis suggested that potentially walking velocity and cadence are influenced by PF spasticity but no other gait or control variables appeared to be influenced by PF spasticity.

Our current results suggest that spasticity may influence the walking velocity and cadence in individuals with MS. Walking velocity can be modulated by increasing step length or cadence. Therefore, it can be inferred that the influence of spasticity on walking velocity would be due to individuals with MS who have spasticity walking at slower cadences. Previous investigations have suggested that spasticity impacts walking velocity because individuals with MS who have spasticity were found to take longer to walk a specific distance than individuals with MS who do not have spasticity.[134] However, this previous investigation did not measure the spatiotemporal kinematics that underlie this decrease in walking speed, therefore, they were unable to comment as to why it took subjects with spasticity longer to complete the walking tests. Another previous investigation did find that individuals with MS who have a higher self-perceived impact of spasticity also had a decreased velocity and cadence.[4] Therefore, it is possible that individuals with MS adopt a slower walking cadence to compensate for the increased spasticity at the ankle, thus also walking at slower speeds.

This investigation was very limited because of the small sample size. Not only did we have one subject with certain MAS PF scores, there was also a very wide spread results for the subjects within a MAS PF score. Therefore, it was difficult to identify trends within the data for evaluating the influence of spasticity upon the gait of individuals with MS. Future investigations with larger sample sizes should be conducted in order to fully understand the influence of influence of spasticity on the gait impairments and motor control deficits of individuals with MS. Also, when conducting these future investigations, it will be vital to consider muscle strength as a contributing factor to the gait impairments and ankle motor control deficits as well. Previous investigations have suggested that muscle strength may influence the mobility of these individuals more than spasticity.[2,107,112,117,124] Moreover, a previous investigation with individuals who have MS found that PF spasticity and ankle weakness only explained less than half of the variance for walking speed and endurance, suggesting that other neuromuscular impairments, such as ataxia or sensory loss, likely contribute to the mobility limitations of individuals with MS.[147] Therefore, it is possible that spasticity may not be the primary limiting factor for mobility in individuals with MS and future investigations should seek to understand the combination of spasticity and other potential factors which may contribute to the impairments in the mobility of individuals with MS.

In conclusion it appears that while the majority of the findings in these investigations are not related to spasticity of the ankle PF muscles, it is possible that this spasticity may influence walking velocity and cadence. However, due to the small sample size and lack of sufficient power for statistical analyses, these conclusions are speculative and should be challenged by future investigations.