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EVALUATION OF ASYMMETRY IN POWER CONTRIBUTION AND MUSCLE ACTIVATION DURING CYCLING IN INDIVIDUALS WITH MULTIPLE SCLEROSIS

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EVALUATION OF ASYMMETRY IN POWER CONTRIBUTION AND MUSCLE ACTIVATION DURING CYCLING IN INDIVIDUALS WITH MULTIPLE SCLEROSIS

A DISSERTATION APPORVED FOR THE
DEPARTMENT OF HEALTH AND EXERCISE SCIENCE

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Abstract

Bilateral asymmetry has emerged as a potential new symptom in persons with Multiple Sclerosis (MS) with previous studies having found significant asymmetries in peak power output (PPO) during single leg cycling and maximal voluntary contraction (MVC) strength. However, asymmetry has only been assessed by testing limbs in an independent manner. **PURPOSE:** The purpose of the current study was to assess bilateral asymmetry in the contribution to total power output production in persons with MS during double leg cycling. **METHODS:** Nine volunteers with MS (Females = 4) and 6 healthy controls (Females= 3) participated in the current study. An initial GXT was performed at a Self-Selected (SS) cadence to obtain VO_2max and PPO. Subsequent GXTs were individualized to allow participants to exercise at relative exercise intensities ranging from 50 to 100% of PPO. Participants performed GXTs at either a SS, High (20% >SS), or Low (20% < SS) cadence. The contribution of each limb to total power output was assessed via dual power meters. Maximal voluntary isometric strength was assessed for the knee extensors of each of the lower limbs. Walking capacity was assessed via the 25ft walk and 6 minute walk tests. Independent t-tests were used to assess differences in descriptive characteristics, isometric strength asymmetry, and walking capacity. Pearson's r correlations were performed to determine the relationship between physiological variables collected during the GXTs and walking capacity. Spearman's correlation was utilized to assess the relationship between Expanded Disability Status Scale (EDSS) score and asymmetry levels. Two-way repeated measures ANOVA were used to detect group x cadence interactions for

physiological variables collected during the GXTs. Differences in the contribution to total power production was assessed using a 3 way mixed factorial ANOVA with between (group) and within subject factors (cadence x intensity). **RESULTS:** No significant differences existed between groups for descriptive characteristics ($p>0.05$). No significant differences existed between groups and cadence for physiological variables. No significant differences were present for contribution to total power production for each limb between groups, cadence, and exercise intensity ($p>0.05$). Significant correlations were found between VO_2max, PPO, asymmetry during SS GXT, and walking capacity during both FTPs. Significant correlations were found when subjects were pooled together and in the MS group alone. Significant correlations were found between EDSS score and asymmetry levels. **CONCLUSIONS:** The current study suggests that exercise intensity may not have an impact on bilateral asymmetry during double leg cycling. However, other analysis techniques may provide additional insights that may be masked by traditional statistical analysis. The use of development of thresholds, such as an asymmetry index of 10%, maybe more appropriate to use in an MS cohort.

Chapter I: Introduction

Multiple Sclerosis (MS) is a chronic neurological disease characterized by the demyelination of axons within the central nervous system (CNS) (1, 2). This demyelination produces scleroses, or plaques, in the white and gray matter of the brain and spinal cord causing the disruption of nerve transmission (1). MS patients often suffer from symptoms related to central and peripheral impairments, generally speaking central impairments involve disruption in the communication to and from the CNS whereas peripheral impairments pertaining to alterations within the muscle itself (3). Due to the heterogeneous nature of the disease symptoms often differ greatly between individuals.

Observations of decrements in both muscle function and performance (as a result of central and peripheral impairments) leading to lower exercise tolerance have been observed in people with MS (4-8). Previous MS related research has shown lower force production, higher levels of muscle spasticity, and a reduction in muscle activation due to central impairments (9-11). Peripheral alterations to muscular tissue associated with MS can include: reductions in muscle enzyme oxidative capacity, slowing of muscular contractile proteins, impairment of the excitation-contraction coupling processes, and muscular atrophy (3, 6, 7, 11, 12). The central impairments and muscular alterations associated with MS can not only cause a reduction in exercise tolerance, but also cause an increase in the perceived difficulty to perform activities of daily living leading to a decrease in quality of life of MS (13, 14).

In addition to symptoms related to central and peripheral impairments recent research has found that MS can affect the body asymmetrically (4-8). Essentially, one

side of the body is more affected than the other side leading to the development of bilateral asymmetry. Bilateral asymmetry has predominately been observed in the lower limbs (4-7). This can be especially detrimental as lower limb movements such as walking and balance can become compromised, leading to an abnormal walking gait and increased likelihood of falls (7, 15, 16). To date only a few studies have been specifically designed with the purpose to observe, assesses, and understand bilateral asymmetry in people with MS. These studies have shown that bilateral asymmetry is present for strength, oxygen uptake, and power output in MS patients (4-8). The protocols used to assess bilateral asymmetry have utilized single leg cycling and single leg maximal voluntary isometric contractions (MVICs) (4-7). By testing the limbs independently it creates a gap in the knowledge regarding how bilateral asymmetry may influence natural bipedal exercises and movements. Until recently the technology to test both lower limbs simultaneously and quantify each limbs contribution to total power output during cycling has not existed. The development of this technology could potentially lead to improved methodology for the assessment and understanding of bilateral asymmetry. A better understanding of the development, progression, and effects of bilateral asymmetry is needed to develop rehabilitation strategies with the purpose of minimizing the effects of MS.

The presence of bilateral asymmetry in traditional double leg cycling has been heavily researched (17). It has been established that a degree of asymmetry exists for peak crank torque, work, and force during pedaling (17-21). The consensus from these studies suggests that both movement and external workload appear to influence bilateral asymmetry. However, the previous studies show a high amount of variability in

asymmetry between subjects and between the protocols utilized (17). Previous research has also examined some potential mechanisms for asymmetry during cycling including muscle activation using electromyography (EMG) (22). Although differences in muscle activation between legs was not present in both healthy controls and trained cyclists this information has not been gathered in a population of individuals with neuromuscular limitations such as MS.

The use of EMG allows for a non-invasive assessment of muscle activation and neural drive (23). An increase in workload is associated with muscle fatigue leading to the synchronization of motor units and an increase in muscle activation due to the recruitment of additional motor units (23, 24). Previous literature has examined bilateral differences in muscle activation during cycling in healthy individuals and found no significant differences between limbs (22). However, this has not been examined in persons with MS where muscle activation may be impaired due to the inhibition of the propagation of action potentials. Additionally, bilateral differences in muscle activation have only been assessed while cycling at a preferred cadence. Little is known how the manipulation of the number of muscular contractions performed will affect this asymmetry while power output remains constant. In theory the increasing or decreasing of the number of muscular contractions performed per minute while power output is maintained will affect the strain placed on the CNS due to alterations in the number and strength of action potentials sent from the soma of the neuron (23). The use of EMG may provide insight into the potential mechanisms of bilateral asymmetry, and potential compensatory mechanisms that may be present in order to possibly maintain symmetry in power production during cycling.

Therefore, the next step in the assessment of bilateral asymmetry in MS patients is to test both lower limbs simultaneously in a natural bipedal movement. Testing in a bipedal movement could provide further insight into how the limbs work together if a bilateral deficit is present that cannot be observed during single leg movements. The development of new technology, double leg cycling could now provide a proper modality for assessment of asymmetry in MS patients. In addition, the use of EMG on both legs during double leg cycling to assess the levels of muscle activation could provide an explanation to the presence of asymmetry.

Purpose

Therefore the purposes of this study were to: 1) investigate whether persons with MS exhibit greater bilateral asymmetry in power production contribution during a double leg graded exercise test compared to healthy controls, 2) investigate potential bilateral differences in muscle activation during double leg cycling in persons with MS, 3) investigate how exercise intensity and cadence selection affect the physical manifestation of bilateral asymmetry in persons with MS.

Research Questions

RQ1: Do persons with MS exhibit greater bilateral asymmetry in power production contribution during a double leg graded exercise test compared to healthy controls?

RQ2: Is there a bilateral difference in muscle activation during double leg cycling in persons with MS?

RQ3: Does exercise intensity and cadence selection effect the physical manifestation of bilateral asymmetry in persons with MS?

RQ4: Do persons with MS exhibit greater bilateral asymmetry isometric strength of the knee extensors compared to healthy controls?

Hypotheses

$H1_a$) Individuals with MS will exhibit greater bilateral differences in power output during a double leg cycling graded exercise test compared to healthy controls.

$H1_0$) Individuals with MS will not exhibit greater bilateral differences in power output during a double leg cycling graded exercise test compared to healthy controls.

$H2_a$) There will be a bilateral difference in muscle activation during double leg cycling in persons with MS.

$H2_0$) There will not be a bilateral difference in muscle activation during double leg cycling in persons with MS.

$H3_a$) The manipulation of exercise intensity and cadence will have significant effect on the physical manifestation of bilateral asymmetry.

$H3_0$) The manipulation of exercise intensity and cadence will not have a significant effect on physical manifestation of bilateral asymmetry.

$H4_a$) Individuals with MS will exhibit greater bilateral asymmetry in isometric strength of the knee extensors compared to healthy controls.

$H4_0$) Individuals with MS will not exhibit greater bilateral asymmetry in isometric strength of the knee extensors compared to healthy controls.

Significance of the Study

To date, no bilateral asymmetry research in MS patients has assessed both lower limbs simultaneously in a bipedal movement. New knowledge in how the lower limbs work together if a bilateral deficient is present will allow for the development of new

rehabilitation programs to reduce asymmetry and thus reduce functional impairments associated with MS. The use of EMG during testing will provide insight to the mechanism of muscular asymmetry, and provide knowledge for the treatment and correction of asymmetry. Minimizing the effects of bilateral asymmetry is important in the maintaining and improvement of exercise capacity and quality of life in MS patients.

Delimitations

The delimitations of this study included:

1. Individuals between the ages of 18-65.
2. Individuals with MS had a physician confirmed diagnosis.
3. Disability status scale score (EDSS) less than or equal to 6.0.
4. Individuals with MS were not using prednisone or other steroids and did not have a steroid dose for at least 3 months prior to testing.
5. Individuals without asymmetric orthopedic limitations.
6. Individuals without metabolic, respiratory or cardiovascular diseases.
7. Individuals all obtained physician's clearance for exercise prior to testing.

Limitations

The limitations of this study included:

1. Since testing occured on a series of dates and fatigue is variable and unpredictable in persons with MS, initial fatigue in multiple sclerosis individuals may differ slightly between testing days.
2. Combinations of medications for symptom management and disease modification may vary slightly between subjects with MS.

3. The same research team conducted all testing for the duration of this study.
4. Testing will be performed at the Department of Health and Exercise Science at the University of Oklahoma in Norman, Oklahoma.
5. Subjects will be recruited from the Norman and Oklahoma City areas through the MS Center for Excellence at the Oklahoma Medical Research Foundation.
6. All possible testing sessions occured at the same time of day relative to each subject.

Assumptions

The assumptions of this study included:

1. All participants provided accurate medical information and health history.
2. All participants were honest when filling out fatigue questionnaires.
3. All participants followed pre-testing guidelines before coming in for testing.
4. All participants exerted maximal effort in all exhaustion tests.

Operational Definitions

1. **Bilateral asymmetry**: significant differences between the left and right side of the body (4).
2. **Body Composition**: the total amount and distribution of fat mass and fat-free mass that makes up a human body (25).
3. **Dual- Energy X-Ray Absorptiometry (DXA)-** uses X-rays at two energy levels and works on the principle that, as X-rays pass through body tissues they are attenuated to a different extent in different types of tissues (26).

4. **Electromyography (EMG)-** the extraction of information from the electrical signal generated by the activated muscle (23).
5. **Graded Exercise Test**: a protocol designed to elicit VO_2max in which workload increases at a defined rate until exhaustion is reached (27)
6. **Kin-Com Dynamometer:** an electromechanical device used to provide resistance during isokinetic and isometric muscular contractions (28).
7. **Kurtzke Expanded Disability Status Scale (EDSS)**- incremental scale used to assess the level of physical disability associated with multiple sclerosis (29).
8. **Matched Control Subjects**: subjects in the control group, which will be matched by average age, gender, and physical activity level to MS subjects (4).
9. **Maximal Oxygen Consumption (VO_2max)**- the maximal amount of oxygen that can be utilized by the muscles during a maximal effort cycling test (27)
10. **Multiple Sclerosis**: inflammatory degenerative autoimmune disease of the central nervous system (2).
11. **Relapsing Remitting:** a clinical course of multiple sclerosis characterized by disease relapses and stages of either full recovery or a deficit after recovery with no progression of disease symptoms during the recovery stages (30).
12. **Quality of Life (QOL):** An umbrella term to describe a number of outcomes important within an individual's life (31).
13. **6-Minute Walk Test (6MW):** This is a functional test and used to assess cardiopulmonary function and has been used in neurological populations. Participants walk as fast and as far as possible without rest or encouragement for 6 minutes (32).

14. **25-Foot Walk Test (25FW):** This is a functional test used to assess an individual's walking ability and leg function based on a timed 25-foot walk. Gait speed has been shown to be a reliable and useful measure of walking ability (33).

Chapter II: Review of Literature

Multiple Sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) characterized by the development of plaques or sclerosis along the myelin sheath of axons resulting in nerve demyelination (34). The detrition of the myelin sheath can cause the attenuation or even the inhibition of action potentials. This disturbance in the propagation of action potentials along the axon can cause a plethora of disabling physical symptoms such as: mobility and coordination issues, optic neuritis, fatigue, and pain (2). MS patients can also suffer from cognitive dysfunction and mood disorders leading to further reductions in quality of life (35, 36). MS symptoms are not homogenous in nature resulting in a wide range of symptoms.

Researchers have recently explored a potentially new symptom of MS. It has been found that MS patients tend to suffer muscle weakness and decrements in strength and cardiovascular performance of their lower limbs (4-8). These decrements are noted to be greater in one limb than in the opposite limb (4-8). These disparities can result in bilateral asymmetry in musculoskeletal performance. The extent to which asymmetry affects individuals with MS and how it impacts function still needs further investigation. The purpose of this review is to provide an understanding of the pathophysiology of MS, bilateral asymmetry in MS, and the impact of bilateral asymmetry on quality of life in MS patients. This will provide support for the proposed project related to assessment of asymmetry during cycling in MS patients. Finally a summary of pertinent literature on asymmetry during cycling will be presented.

Multiple Sclerosis

Axons of neurons within the CNS are coated in a fatty sheath known as the myelin sheath (1, 2). The myelin sheath provides insulation for the axon, and helps increase conduction velocity of action potentials down the axon (37). MS causes the deterioration of the myelin and the loss of both neuronal axons and myelin producing oligodendrocytes (2). The demyelination of the axons causes the development of sclerosis, or plaques, in the white matter of the brain and the spinal cord that disrupt nerve transmission as well as inhibit the formation of new myelin (38). The attenuation or inhibition of nerve transmission can lead to a wide range of debilitating physical symptoms leading to decreases in quality of life in MS patients. There are several

theories to the cause of MS, but three main schools of thought for the pathophysiology of MS have risen: genetic, environmental and infectious agent, and autoimmune.

Genetic

A genetic predisposition has been established for MS through: familial aggregation (39), high monozygotic concordance rate (31%) (40). The lifetime incidence of MS is 0.1% in a normal population, but this increases to 3% for siblings of MS patients (41). The risk of incidence increases to 25% for the twin of an MS patient (41). The genes that contribute to MS susceptibility have not yet been identified, but efforts have been taken to identify potential risk alleles that may predispose for MS. Linkage studies have identified human leukocyte antigen (HLA) alleles as MS risk genes (42, 43). The findings of these studies have been interpreted with caution to due flaws in the techniques used. However, using association studies, which exam single nucleotide polymorphisms on a genome-wide level, Interleukin 2 Receptor Subunit Alpha (IL2Ra), Interleukin 7 Receptor (IL7R), and Lymphocyte Function Associated Antigen 3 (LFA-3) genes were newly identified as risk alleles for MS (44). Further studies are needed to confirm current genetic findings and to identify new genes.

Environmental and Infectious Agent

The prevalence of MS has been observed to increase with increases in the distance from the equator (29). Due to the difficult nature of ecological case-control studies it is unclear whether environmental factors elevate the risk of an individual or an entire population for the development of MS.

Infectious diseases such as Chlamydia pneumonia , human herpes virus-6 (HHV-6), and Epstein-Barr virus (EBV) have been hypothesized as causative agents of

MS. These hypothesis have been based on the isolation of genetic material or proteins of microbial agents from MS lesions (45-47). Recently, in post-mortem brain specimens from MS patients genes and proteins from EBV associated with both latent form and reactivated form of the virus have been identified (47). However, these findings have not yet been reproduced by other groups and should be interpreted with caution. Some researchers believe the relationships between these infectious agents and MS is merely casual and not direct with the infectious agents providing the appropriate cascade for an autoimmune reactive response against the CNS (48).

Autoimmune Response

The myelin sheath of neurons not only increase conduction velocity along axons but also contributes to the protection and health of the axon (49). The main characteristic of MS is the attacking and deterioration of this myelin sheath. It is generally well accepted that the pathology of MS begins with a breach in the blood-brain barrier allowing for the influx of autoimmune agents into the CNS, and initiating an inflammatory response (2). One hypothesis suggests that individuals with MS are genetically predisposed for the breach in the blood-brain barrier (50). While others believe that some forms of systemic infection may cause the up-regulation of adhesion molecules on the endothelium of the brain and spinal cord thus allowing autoimmune agent to enter the CNS (48).

Among the agents that have been suggested to be involved in the inflammatory response in the CNS are autoreactive T cells (CD4+ and CD8+). These cells react to antigens located in the myelin of the CNS and will result in demyelination (51-53). Healthy individuals and MS patients possess similar amount of myelin reactive T cells.

However, an MS patient exhibits an activated phenotype while those from healthy individuals appear to have a naïve phenotype (54, 55). T cells believed to be involved in the inflammatory response have been suggested to be type 1 helper T cells that produce interferon-y which has been shown to mediate inflammatory responses (53). Once the T cells enter the CNS, they begin to attack the myelin sheath and begin to create plaques or sclerosis at the sites of attack (56). Due to the heterogeneity of MS no distinct pattern of sclerosis development has been observed and is considered unpredictable (48).

In addition to the development of plaques on the myelin sheath, MS can cause axonal injury (57). Pathological changes in the axons can be detected early in the disease progression by the accumulation of amyloid precursor protein due to inflammation (58). In an attempt to reestablish normal conduction there is an increase in sodium entry into the axon, followed by the reversal of the sodium-calcium exchanger, which may cause axonal injury or even neuronal degeneration due to the influx of calcium (57). Axonal injury continues to increase with the progression of the disease with some old lesions having an axonal loss of more than 80% (56). The cumulative loss of axons correlates with irreversible disability (48).

Remyelination occurs frequently in the plaques of MS patients but is ineffective in reestablishing its normal function (2). Remyeliation often occurs in plaques that develop early in the disease process but are often restricted to the periphery of inactive plaques forming shadow plaques (59). The extent of the repair to the myelin sheath is related to survival of oligodendrocytes within the plaques. Often very few oligodendrocytes survive, but numerous oligodendrocyte precursor cells often remain

(60, 61). These cells can re-express developmental genes and produce myelin in demyelinated areas.

Symptoms

The symptoms associated with MS vary greatly between patients (1). It is still unclear as to how the site of plaques, the number of plaques, and the stage at which the plaques are in affect symptoms. However, it is clear that many symptoms impair the ability of MS patients to exercise and perform activities of daily living (3, 13, 62). Symptoms are typically classified as either being central (alterations within the CNS) or peripheral (alterations within peripheral musculature).

Central Symptoms

Reduced central activation has been identified as a primary consequence of MS (63). Muscle fatigue has been correlated with an increase in central drive, suggesting this as compensatory mechanism to overcome the lack of central activation (63). Reorganization of descending axons may be occurring as indicated by the increase in central motor drive in the presence of decreased central activation (63). Previous research has shown impairments in motor unit firing rates, motor unit activation, and slower muscle contraction speeds in MS patients, all of which could have a detrimental effect on strength and function (7).

Ng et al. 1997 (63) evaluated central motor drive in individuals with MS during voluntary dorsiflexion muscle contraction using EMG on the tibialis anterior muscle. It was observed that central motor drive was increased in MS patients compared to healthy controls during submaximal contractions ranging from 10 to 70% of an individual's maximal voluntary contraction. It was also noted that the disability status

and the slope of the EMG/force relationship of the MS individuals were highly correlated ($r = -0.87$, $P < 0.001$). The researchers observed that even the MS individuals without any visible weakness (limping) still showed an increased motor drive. The findings of this study suggest that central drive alterations are present and occur before any physical manifestations are visible.

Ng et al. 2004 (9) performed another study to investigate central motor impairments in conjunction with peripheral muscle adaptations thought to be a result of MS. Central impairment was assessed by having eighteen MS subjects and eighteen healthy controls perform a voluntary maximal isometric contraction (MVIC), followed by another MVIC with additional electrical stimulation. The central activation ratio was determined by dividing the maximal voluntary force divided by the maximal force produced with superimposed electrical stimulation. If more force is produced by the muscle during electrical stimulation it suggests the presence of central impairments. The current study examined the ankle dorsiflexion and found that MS patients showed 32% less maximal force production (N) than healthy controls (CON vs. MS: 157 ± 12 vs. 115 ± 15; $p = 0.03$). However there was no significant difference between MS patients and healthy controls for force produced (N) with the electrical stimulation (CON vs. MS: 122.1 ± 11.3 vs. 125.9 ± 12.8; $p = 0.82$). It was therefore concluded that reductions in the central activation ratio within the MS patients was a result of incomplete motor unit recruitment.

Assessing impairments in central activation is a difficult task due to the intertwined nature of the CNS and peripheral nervous system (PNS). Previous research has shown though that the ability to perform rapid successive movements of the foot is

a simple test for the assessment of lower extremity motor function in the upper motor neurons (64). This test highlight voluntary maximal rate of force production (64). The "toe-tap" test requires both motor unit recruitment and rate coding to perform the maximal amount of successive rapid toe tapping in 10 seconds (64, 65). It has been suggested that the "toe tap" test can give an index of motor production and additionally an indirect measure of central drive in clinical populations (65, 66).

Peripheral Symptoms

Although MS is a CNS disease, a number of alterations within the peripheral musculature have been observed. Previous research has shown decreases in oxidative capacity, decreased oxidative enzyme activity, slowing of muscle contractile properties, impaired excitation contraction coupling, and muscle atrophy (3, 7, 12, 67).

Sharma et al. (3) evaluated the intramuscular components related to the development of peripheral fatigue in twenty eight MS patients and fourteen controls. A nine-minute intermittent electrical stimulation protocol of the tibialias anterior was used to assess force production, intracellular pH, and phosphocreatine (PCr) levels. They observed greater decreases in force (MS vs. CON: 64.8 ± 3.6% of initial vs. 86.1 ± 2.6% of initial, $p < 0.01$) PCr (MS vs. CON: declined to 16.2 ± 2.7 vs. 25.3 ± 1.8 mmol/L; $p > 0.01$), and pH (MS vs. CON: 6.76 ± 0.07 vs. 6.91 ± 0.05 $p > 0.05$) in MS patients when compared to healthy controls with no significant decreases in the amplitude of compound muscle action potentials. This finding indicates that neuromuscular transmission was not a limiting factor and fatigue was developed in the peripheral musculature. The researchers therefore concluded that both central mechanisms, upper motor neuron dysfunction, and peripheral mechanisms, impaired

excitation contraction coupling, are related to the development of fatigue in MS patients.

Diagnosis

It is estimated that 0.1% of the population in temperate climates suffers from MS. With some 250,000 to 350,000 people in the US are diagnosed with MS (2). It is considered a disease of young people with median age of diagnosis being 29 years of age, and the female/male ratio of diagnosis is roughly 3:1 and may be increasing (1, 68). It is the second most common cause of disability in young adults, and it is one of the costliest chronic diseases, with total annual costs per affected individual exceeding US$50,000 (2007), which is similar to that of congestive heart failure (1, 69, 70) . 50% of MS patients require a cane to walk 15 years after the disease onset (2, 71). Currently there is no definitive diagnostic test or tool Detection of MS involves the use of several diagnostic tools including magnetic resonance imaging, cerebrospinal fluid analysis, neurological examination, medical history analysis, evoked potential responses to sensory stimulation, and blood tests to rule out diseases with similar symptoms. In order to ensure a definitive diagnosis of MS a person must present with: two or more areas of demyelination, evidence of lesions in the white matter, increased immunoglobin G synthesis in the spinal fluid, and two or more neurological deficits(72).

Bilateral Asymmetry

It has been shown that MS can affect the body in an asymmetrical nature, where one side of the body is more compromised than the other. (4, 5, 7, 8). Researchers have noted differences between lower limbs in both strength and cardiovascular measures (4-8). These disparities between lower limbs can have detrimental effects on activities of

daily living that require bilateral function, balance, or a combination of the two such as walking (73). These disparities could also place MS patients at a higher risk for falls and further decreasing quality of life (74). Bilateral asymmetry is a relatively new area of research in MS patients, with the current state of the research being limited.

One of the first studies to observe bilateral asymmetry in an MS patient was a case study conducting by White and Dressendorfer in 2005 (8). The case study examined bilateral differences in oxygen uptake in one female subject with MS. The subject performed a traditional double leg VO_2max test followed by two single leg VO_2max tests. It was found that the during the single leg VO_2max test, the right leg achieved a VO_2max equivalent to 85% of that achieved during the double leg test while the left leg only achieved 60% of the double leg test. It was also observed that the VO_2peak (Right vs. Left: 49.3 vs. 34.7 ml/kg/min), heart rate (Right vs. Left 158 vs 134 bpm), and pulmonary ventilation (Right vs. Left: 81.5 vs. 55.6 L/min) were 30% lower during the single max test for the left leg compared to the right leg. The researchers suggested that due to a large cardiopulmonary reserve seen during the single leg test of the left leg, performance differences between limbs could be contributed to limitations in strength or O_2 extraction rather than O_2 delivery. It is also noteworthy that the subject was a former competitive runner, and still maintained a rigorous exercise program even after MS diagnosis. The researchers suggested that due to her training program her right limb may have experienced increased strength and O_2 extraction as a compensatory mechanism to offset limitations in her left limb.

Chung et al. 2008 (7) examined differences in functional measurements between the lower limbs of MS patients. Subjects performed three MVICs and three isotonic

contractions with a resistive load of 45% of the peak isometric torque for both knee extensors and dorsiflexors. No significant differences were observed in the isometric asymmetry score for both the control and MS subjects in for knee extensors (CON vs. MS: 13.9 ± 12.7 vs. 15.7 ± 11.5%; $p = 0.72$) and dorsiflexors (CON vs. MS: 8.5 ± 5.3 vs. 10.1 ± 7.7; $p = 0.56$). No significant differences were observed in dorsiflexors power asymmetry score between groups (CON vs. MS: 14.7 ± 15.4 vs. 16.7 ± 12.1; $p = 0.73$). However, significant differences in the knee extensor asymmetry score was observed between the groups with the MS group having a significantly greater asymmetry score compared to the control group (CON vs. MS: 9.2 ± 6.9 vs. 21.5 ± 16.2; $p = 0.02$).

A major issue regarding research concerning bilateral asymmetry in MS patients is the designation or classifying of the legs for comparison. Most studies have compared the legs based on right/left or dominant/non-dominant (7, 9, 75). However, bilateral asymmetry is not restricted to weakening the non-dominant side of the body (4). Asymmetry also does not affect the same side of the body for every individual. Classifying and comparing limbs based on these criteria may skew results and hide the presence of asymmetries. It has been recommended to classify and compare limbs using "more-affected" and "less-affected" limbs when testing for asymmetries (4). One of the first studies to use to classification of limbs was Larson et al. 2013 (4). The researchers examined the presence of bilateral asymmetries in MVICs and single-leg incremental cycling in eight MS subjects, diagnosed with relapse remitting MS, compared to seven healthy controls. It was observed that the MS group possessed significantly greater differences between limbs in MVIC compared to the control group (MS vs. CON: 8.34 ± 5.7 vs. 2.1 ± 6.1 kg; $p < 0.01$). Using a ramp protocol, the researchers observed

significantly greater differences between limbs in peak workload (MS vs. CON: 18.1 ± 14.0 vs. 0.57 ± 5.1watts; $p < 0.01$) and VO_2peak (MS vs. CON: 3.1 ± 1.9 vs. 0.83 ± 2.0 ml/kg/min; $p < 0.05$) in the MS group compared to the Control group during the single-leg incremental cycling test to failure. To ensure differences in lower limb performance was not due to differences in lean tissue mass, DXA scans revealed no significant differences in lean tissue mass between limbs ($p > 0.05$). To highlight the heterogeneity nature of bilateral asymmetry and further justification for the use of the "more-affected/less-affected" limb classification, it was observed that 4 out of the 8 subjects' significantly weaker limb was their dominant limb.

Building upon the observations in bilateral asymmetry in cardiovascular performance in MS patients, Larson et al. 2014 (5) performed another study to examine endurance performance in lower limbs of eight MS patients, diagnosed with relapse remitting MS, and 7 healthy controls. Subjects performed a whole body (double leg) oxygen uptake test using a cycle ergometer. Subjects then performed a five minute single leg submaximal fixed load cycling test. Fixed workload was set at 20% of the peak workload achieved during the whole body oxygen uptake test. It was observed that the MS subjects performed significantly more work (KJ) with the less-effected limb than the more-effected limb (less-effect vs. more effected: 6.4 ± 1.7 vs. 4.7 ± 2.5 kJ; $p = 0.02$), while no significant differences were observed between limbs in the Control group (less-effect vs. more effected: 9.2 ± 3.2 vs. 9.1 ± 3.2; $p = 0.36$). The difference between limbs was also significantly greater for work performed in the MS group compared to the Control group (MS vs. CON: 1.7 ± 1.6 vs. 0.1 ± 0.4 kJ; $p = 0.02$)

The research in bilateral asymmetry in MS patients has revealed significant asymmetries between lower limbs for strength measurements and cardiovascular responses (4-8) All of the previous research has isolated lower limbs and tested them independently of each other. However, the modalities tested have been bipedal movements in nature. Performing testing using modalities such as single leg cycling may not necessarily provide data that can be interpreted and applied to functions that require limbs to function simultaneously together. Therefore, future research should focus on testing lower limbs with more natural modalities (walking, double leg cycling) in order to examine how the more-affect and less-affected limbs work together during bipedal movements.

Effects of Bilateral Asymmetry on Function

The full effects of bilateral asymmetry on quality of life and activities of daily living are not fully understood yet. However, research has shown that MS patients with bilateral asymmetry have slower 25 foot walk times at both brisk and normal paces, take more steps during 25 foot walk test, show great amounts of sway during postural control tests, and possess asymmetrical hip bone density (7, 76).

Chung et al in 2008 (7) observed significantly greater levels of bilateral asymmetry in the knee extensors in MS patients (CON vs. MS: 9.2 ± 6.9 vs. 21.5 ± 16.2; $p = 0.02$). Postural stability was also tested in this study using two adjacent force plates to record ground reaction forces underneath each foot while subjects stood quietly for 20s with their eyes directed forward. Data from the force plates was used to calculate center of pressure variability (CoP_v) in the anteroposterior (AP) and mediolateral (ML) direction and bilateral distribution of body mass. The researchers

observed that MS patients displayed a significantly greater COP_v in the AP direction compared to controls (7.52 ± 3.02 and 4.33 ± 1.79mm, respectively; $p = 0.005$. The loading asymmetry score between limbs was significantly greater in MS compared to controls (CON vs. MS: 6.0 ± 3.0 vs. 10.5 ± 6.9; $p = 0.05$). The researchers observed a high correlation between limb-loading asymmetry and postural sway in both the AP (r = 0.62, $p = 0.001$) and ML (r = .80, $p = <0.001$) directions suggesting that load distribution beneath the feet plays a role in postural control and stability. No relationship was observed between limb-loading asymmetry and knee extensor asymmetry ($p > 0.05$) in the MS patients, but a significant association between knee extensor power asymmetry and CoP_v in the AP direction (r = 0.58, $p = <0.01$) did exist. Although no relationship appeared to exist with bilateral asymmetry in knee extensors and asymmetry in limb loading there appears to be a relationship in limb loading and postural control, which a relationship did exist with knee extensor asymmetry, it cannot be fully concluded that muscle asymmetries do not contribute to asymmetries in limb loading. Further research is needed to fully understand the interaction between muscle asymmetries, postural control, and limb loading asymmetry.

In the same study by Chung et al. in 2008 (7), MS patients performed a 25 foot walk test at a normal and brisk pace. It was observed that the MS patients required more time (CON vs. MS: 6.8 ± 0.7 vs. 9.0 ± 1.8 seconds; $p = <0.001$ & 4.8 ± 0.4 vs. 6.6 ± 1.5; $p = <0.001$) and more steps (CON vs. MS: 12 ± 1 vs 14 ± 2; $p = 0.001$ & 10 ± 1 vs. 12 ± 2; $p = <0.001$) to walk 35ft at both the normal and brisk paces, respectively, compared with controls. It was also observed at a significant relationships existed between knee extensor asymmetry score and both normal (r = 0.63, $p = < 0.001$) and

brisk pace (r = 0.61, p = < 0.001) walk times, with the greater the asymmetry the slower the times. This finding suggests that power asymmetry in the lower limbs may negatively affect gait and walking speed.

Larson et al. (4) observed significant bilateral differences in peak VO_2 and peak workload between legs of MS patients using a single leg graded exercise test. Subjects also performed a six minute walk test prior to all testing. It was observed that subjects covered significantly less distance when compared to controls (MS vs. CON: 474.3 ± 93.1 vs. 626.9 ± 94.0 meters; $p < 0.05$) . It was also observed that a significant relationship between six minute walk test performance and leg differences in peak workload (r= -0.65, $p < 0.05$) with larger differences between legs in peak workload resulted in less ground covered during the six minute walk test. The researchers concluded that bilateral differences could be the reason for a large amount of the limitations in functional capacity, but more research is needed to support this conclusion.

Conventional practices for assessing lower-extremity bone mineral density (BMD) of only one of the proximal femoral neck of the hip and using this measurement to represent the BMD of the contralateral hip due to the negligible differences in BMD between dominant and non-dominant or right and left hips (76-80). Due to lower limb bilateral asymmetry, Larson et al. 2011 (76) examined the BMD of both of the proximal femoral hip in MS patients. The researchers observed the proximal femoral neck of the more-affected limb showed lower BMD compared to the proximal femoral neck of the less-affected limb. If the conventional method for assessing BMD of the proximal femoral neck of the hip had been used on the current sample of MS patients nearly 13%

of the participants would have been misclassified or experienced undetected bone loss if the less-effected limb had been scanned. The researchers suggested that the BMD differences observed could be related to atypical bone remodeling associated with low or unusual load-bearing status, muscle weakness, and atrophy.

More research is needed in the area of bilateral asymmetry in MS patients as a whole, but more emphasis needs to be placed on understanding the consequences to overall health and activities of daily living.

Assessment of Asymmetry via Double Leg Cycling

The presence of asymmetry in cycling has been explored with findings showing some degree of asymmetry in: force, crank torque, work, and power output (17-21, 81). Researches have also examined and suggest that movement speed and external workload appear to influence bilateral asymmetry. However, there is a high variability of asymmetry indexes (level of asymmetry) between subjects and protocols used for evaluation. No definitive protocol has been established to effective evaluation of bilateral asymmetry during cycling.

Carpes et al. in 2007 (82) used six sub-elite competitive cyclists to examine asymmetries in crank torque during a 40km time trial (TT). Subjects were asked to complete the 40km TT using a self-selected strategy to complete that distance in the quickest time possible. The data was divided four stages of equal time according to the total time to complete the TT. Comparisons between legs for crank torque were based on dominant/non-dominant classification of the legs. Although not statistically significant, exercise intensity was higher in stages 1 and 4 compared to stages 2 and 3, with the highest intensity in stage 4. A significant correlation (r=0.97) was observed

between exercise intensity and peak crank torque. The researchers observed a significantly greater peak crank torque during the 4th stage of the TT when compared to the other three stages. A significant reduction in crank torque was observed in stages 2 and 3 compared to stage 1 and stage 4. No significant differences in crank torque were observed between stages 2 and 3. When examining the asymmetry in crank torque production as in indicated by AI% [(Dominant leg-Nondominant leg)/Dominant leg) X 100], an AI% of $\geq$ 10% was considered asymmetrical. It was observed that during stages 2 and 3 an AI% of 13.51±4.17% and 17.28±5.11% respectively and considered asymmetrical. However, during stages 1 and 4 no asymmetries in peak crank torque were observed. It was also noted that the dominant leg produced significantly greater peak torque than the non-dominant leg during stages 2 and 3. Significant levels of asymmetry in crank torque were noted in stages 2 and 3 when crank torque was significantly lower than stages 1 and 4. During stages 1 and 4 no significant levels of asymmetry were observed in accordance with significantly higher levels of crank torque. These findings suggest that asymmetry associated with the dominant leg changed systematically with crank torque and exercise intensity, with the higher levels of crank torque and exercise intensity showed lower levels of asymmetry.

The influence of pedaling rate on bilateral asymmetry in cycling has been examined by several researchers. Daly et al. in 1971 (18) examined how three different cadence rates (40, 70, and 100 rpm) performed at resistance setting of 1.6, 2.2, and 3.8 kilopond on a monarch cycle ergometer would affect bilateral asymmetry. Subjects were considered to be recreational cyclist. Legs were classified and compared in two different ways: based on dominant/non-dominant limb and strength dominance based on

which leg applied more force to the pedals. No significant effects for speed or resistance changes were shown between conditions when using strength dominance for comparison. However, when using leg dominance for comparison it was shown that a main effect existed for speed although no directional trend existed. The researchers observed that one leg tended to generated more crank torque than the other leg. However, no trend in terms of leg dominance seemed to exist when analyzing crank torque asymmetry. The findings of the current study should be interpreted with caution; the day to day reliability of the index of asymmetry was 0.47.

Smak et al. (21) examined whether bilateral asymmetry in cycling changed systematically with pedaling rate. Eleven male competitive cyclists were recruited for this study and performed five different cycling trials at five different pedaling rates (60, 75, 90, 105, and 120 rpm) all at 250 watts. Asymmetry was examined by calculating differences in average positive power (%AP), average negative power (%AN), and average crank power (%AC). Simple linear regressions were used to assess the relationships between the subject sample and these measures as well as the individual subject and asymmetry measures. For the subject sample only %AN exhibited a significant linear relationship with pedaling rate, with asymmetry decreasing as pedal rate increased. The dominant leg was observed to contribute significantly greater average crank power than the non-dominant leg, but the non-dominant leg contributed significantly greater average positive power and average negative power than the dominant leg. No significant linear relationships existed for %AP, %AN, and %AC with pedaling rate. The researchers concluded that the high variability in preferred

pedaling rate with the sample caused different systemic changes in asymmetry with pedaling rate.

The effect of bilateral asymmetry on cycling performance is not fully understood yet. A study by Liu et al. in 2012 (83) examined the level of bilateral asymmetry in across different age group (Young Children (YC)= 5-7years, Old Children (OC)= 8-10years, Adult (AD)= 24-30years) and its effect on cycling performance. Participants performed five 15-second pedaling trials at five randomized target cadences (40, 60, 80, 100, and 120 rpm). Asymmetry was determined by calculating the asymmetry index (AI) used in previous studies using the average angular velocity of the ergometer's crank at 90 and 270 degrees in the crank cycle (90 degrees corresponds to the maximum mechanical advantage for pushing with the right leg, and 270 degrees for the left leg). Cycling performance was measured by calculating root mean square error (RMSE) and was an indication of how closely the participant's performance matched the target cadence. Higher RMSE indicated poorer cycling performance. Bilateral asymmetry was highest in the YC, followed by the OC, and AD groups. It was observed that YC showed significantly higher RMSE than AD at all cadences, and had significantly greater RMSE when compared to OC all at cadences except for 80 and 120 rpm. The OC group had significantly greater RMSE than AD at all cadences except for 40 and 120 rpm. A significant positive correlation between AI and RMSE was observed for all cadences. The researchers concluded that higher AI was related to poorer cycling performance as indicated by higher RMSE. However, this conclusion should be interpreted with caution. No actual performance measures such as: time required to cover defined distance or distance covered in a defined time were

measured. Interpretation of performance was based on the ability to sustain a preselected rpm for 15 seconds; little evidence exists to show that this test is a valid measure of performance.

In summary the findings associated with the effect of pedaling rate on asymmetry and the relation of leg dominance on asymmetry are somewhat mixed. However it seems to be clear that an increase in power output results in a decrease in bilateral asymmetry. A clear definitive protocol for the determination of bilateral asymmetry is still needed. Previous studies have predominately used a series of steady state trials to observe asymmetry during cycling with little known how a continuous increase in exercise intensity will affect asymmetry. Previous studies have also predominately used crank torque to examine asymmetry. Technology now exists to examine the power output of each leg simultaneously together to understand each legs contribution to total power output. This understanding would make the creation and application of exercise programs designed to reduce asymmetry more conceivable as most training programs for cyclist are based on power output (watts). Further research is still needed on the level of asymmetry present during cycling, with studies showing that a range of 5 to 20% (17) may exist in bilateral performance, in cyclist and several subcategories of non-cyclist. With many studies using different methods for the identification of asymmetry (>10%, AI%, etc.) a valid method is still in need of development.

EMG during Cycling

It had been speculated that asymmetries seen during cycling could potentially be explained by differences in muscle activation between legs. Although several studies

have examined muscle activation during cycling, to the knowledge of the current researcher only one study has examined differences between legs in muscle activation. To explore this theory Carpes et al. in 2011 (22) examined muscle activation of the gastrocnemius, biceps femoris, and vastus lateralis of both legs during both incremental and constant load exercise in both cyclist and non-cyclist. Both groups completed an incremental exercise test to failure. Gas exchange and muscle activation, via EMG, were analyzed according to 40, 60, 80, and 100% of the individual's maximal power output. 60 to 90 minutes following the incremental exercise test subjects completed a constant load trial at 70% of the second ventilator threshold observed during the incremental exercise test. In both groups muscle activation of the vastus lateralis and biceps femoris increased significantly as the exercise intensity increased in both the dominant and non-dominant legs. There was no difference in the magnitude of muscle activation between the dominant and non-dominant leg in both groups. The similarity between legs supports the proposed role of fatigue on bilateral differences. It is proposed that in an increase in bilateral output could facilitate excitability and neural coupling by inter-hemispheric cortical communication which is known to be a mechanism for the reduction of lateral differences (22, 84, 85). However, higher variability in the muscle activation was seen in both groups. In the cyclist group high variability was noted for the non-dominant leg while no clear influence of leg dominance was observed in the non-cyclist group. The variability seen within the cyclist group was significantly lower than that of the non-cyclist group and could be related to improved muscle synergy seen through long term training resulting in more precise and accurate ability for force control (22, 86). The researchers concluded that

the asymmetries in favor of the dominant or preferred foot seen during cycling are not directly related to the magnitude of muscle activation.

Summary

MS is a neurodegenerative disease that results in the demyelination of axons in the CNS. To date the exact cause of the disease is still unknown, but many promising theories exist. Due to the heterogeneity nature of MS patients can suffer from a wide variety of symptoms. Recently bilateral asymmetry has been identified as a symptom associated with MS. Research is still needed to develop proper methodology for testing asymmetry as well as understanding the cause of the asymmetry and the impact it can have on the health and well-being of the subject. Most of the current research on asymmetry in MS patients test performance measures in the limbs independently, and this methodology may not be an accurate depiction of the relationship and functionality of the limbs when working together. Cycling presents a potential modality to test for asymmetry in the lower limbs while the limbs are working in sync. Using EMG during cycling will also help to understand if the cause of the asymmetry, if present, is due to muscle activation.

CHAPTER III: METHODOLOGY

This chapter presents the methodology for this study. Methods include a description of the research subjects, research design, data collection procedures, instrumentation, and data analyses.

Sample Size Calculations

Based on single leg cycling data from the current research group's lab and previous literature on differences between limbs during double leg cycling (22) an effect size of 0.8 was chosen. Using and effect size of 0.8 and an α of 0.05 a total of 10 subjects were required for each group to achieve a statistical power of 0.8.

Participants

Nine MS patients (MS group) ages 18 to 65 were recruited for the current study. Additionally, 6 non-MS patients (Non-MS group) were recruited for the current study. The Non-MS group was matched by age, height, weight, and physical activity level with the MS group. All participants signed a consent form approved by the University's Institutional Review Board (IRB). Medical history and physical activity levels were determined using an approved questionnaire. MS participants were recruited through the Oklahoma Medical Research Foundation's MS Excellence Center, and matched Non-MS participants were recruited from the University of Oklahoma as well as the Norman and Oklahoma City metro area.

Inclusion Criteria

In order to be eligible for this study subjects had to fit the following requirements.

1. Individuals with MS had a physician's MS diagnosis of the relapsing-remitting progression and were free from relapse for the three months prior to testing. A relapse is defined as a period of worsening symptoms lasting longer than 24 hours.
2. Both the persons with MS and those in the Non-MS group obtained a physician's clearance for all exercise tests included in the study prior to testing.
3. Individuals with MS had an Expanded Disability Status Scale (EDSS) score of 6.0 or less (minimal to moderate disability—may need intermittent or unilateral aid to walk 100m).
4. Individuals on the medication prednisone or who have had a steroid dose less than 3 months prior to testing were excluded.
5. Individuals with any past lower limb orthopedic asymmetries (hip replacement, knee surgery, etc.) or other significant lower limb bilateral asymmetries were excluded from participation.

Exclusion Criteria

Subjects with the following characteristics were not included in the study:

1. Individuals with orthopedic injuries that would create asymmetry.
2. Individuals with metabolic, cardiovascular, or respiratory diseases.
3. Individuals with multiple sclerosis who are not relapsing remitting and have an EDSS score greater than 6.0.
4. Individuals with multiple sclerosis who have experienced a relapse sooner than 3 months prior to testing.
5. Individuals who have had a steroid dose less than 3 months prior to testing.

Research Design

This study utilized a mixed factorial design. Participants were familiarized with all equipment and testing protocol prior to testing. Participants performed a graded exercise test (GXT) to task failure at a self-selected cadence. Participants then performed three additional GXTs, wearing EMG electrodes, with stages that corresponded to 50, 60, 70, 80, 90, and 100% of the peak power output achieved during the GXT. Each of the three individualized GXTs was performed at a randomly chosen cadence that corresponded to either: self-selected cadence, 20% greater than self-selected cadence (high), and 20% lower than self-selected cadence (low). Additionally, participants performed a series of maximal voluntary isometric contractions (MVCs) to assess isometric muscular strength. Functional capacity was assessed via the 6 minute walk test and the 25 foot walk test. A rest period of at least 48 hours between testing for all participants was required. Each participant completed 6 laboratory visits.

Table 1. Visit Protocol Outline

Protocol		Time
Visit 1	1. Informed Consent 2. Medical History Questionnaire 3. PAR-Q 4. Symptomatic Fatigue assessment 5. DEXA Scan 6. Graded Exercise Test familiarization 7. Functional Assessment familiarization 8. Maximal Voluntary Isometric Contraction Familiarization	Approximate Time: 120 minutes
Visit 2	1. Graded Exercise Test (self-selected cadence) 2. Verification Test	Approximate Time: 60 minutes
Visit 3	1. Individualized Graded Exercise Test (cadence randomly assigned)	Approximate Time: 60 minutes
Visit 4	1. Individualized Graded Exercise Test (cadence randomly assigned)	Approximate Time: 60 minutes
Visit 5	1. Individualized Graded Exercise Test (cadence randomly assigned)	Approximate Time: 60 minutes
Visit 6	1. Maximal Voluntary Isometric Contraction Familiarization 2. Functional Assessment (6 minute walk and 25 foot walk)	Approximate Time: 60 minutes

Control Variables

Testing was performed at approximately the same time of day throughout the study relative to each subject's first visit. Subjects were asked to abstain from alcohol, caffeine, exercise and smoking for 12 hours prior to each visit and consumed a light meal 2-3 hours prior to testing. Hydration status was assessed using a refractometer (model CLX-1, VEE GEE Scientific Inc., Kirkland, WA) to determine urine specific gravity (USG) prior to all exercise tests using. A USG value of no greater than 1.028 was required before testing can be commenced. If a USG greater than 1.028 was determined subjects will be instructed to consume water, and USG will be reassessed.

Questionnaires

Symptomatic Fatigue Assessment

Each individual with MS was asked to keep an hourly fatigue diary everyday on and between testing sessions and filled out a questionnaire on test days in order to determine daily symptomatic fatigue. A specific fatigue decision tree was used in order to assess if changes in fatigue are significant enough to reschedule testing. If changes in symptomatic fatigue were substantial between testing days (changes of 10 or more points on the MFIS and/or persistent low energy levels for multiple days based on the RFD), the subject was asked to return to the lab on another day for testing.

Modified Fatigue Impact Scale (MFIS)

The MFIS is a 21-item questionnaire using a summated rating Likert scale that examines the impact of fatigue on everyday life (87). This questionnaire measures physical, social, and cognitive aspects of symptomatic fatigue and allows for the calculation of a global score which was used in fatigue evaluation (88).

Rochester Fatigue Diary

Rochester fatigue diary (RFD) was filled out for everyday of participation in the study including non-testing days. The RFD allows the subject to rate fatigue on a visual analog scale for every hour of the day (89). This scale is especially advantageous because it specifically assesses reduced energy levels. Past research has shown that subjects are better able to assess energy levels over short periods of time than more complex aspects of fatigue over longer time periods (89). Fatigue levels between visits were evaluated prior to exercise tests.

Maximal Voluntary Isometric Contractions

The maximal voluntary isometric contraction (MVC) of the knee extensor muscles were assessed using a dynometer (KinCom model: KC125AP, Isokinetic International, East Ridge, TN 37412). Subjects were seated with hip and knee angle set at 70°. Participants were asked to perform a series of warmup isometric contractions at submaximal intensities with 2 to 3 minutes of rest between contractions. Following the warmup, participants performed 3 MVICs lasting 3 seconds each with 3 minutes of rest between contractions. Both legs were assessed, and the order was randomly selected.

Strength Asymmetry Score

Strength asymmetry scores were determined for power as:

$$Strength\ asymmetry\ score = \left[1 - \left(\frac{Power\ of\ Weaker\ Limb}{Power\ of\ Stronger\ Limb}\right)\right] 100$$

where the strength ratio was the value for the weaker limb divided by the value for the stronger limb. Zero percent asymmetry indicated even distribution of power across limbs, and 100% indicated maximal asymmetry (7).

25-Foot Walk Test

The 25-foot walk test has been an assessment tool used by researchers and clinicians to assess disease progression in MS patients (13, 41, 78, 90), and has been included in the Multiple Sclerosis Functional Composite score (91). Testing procedure involved participants starting in a standardized standing position, and walking 25-foot as quickly as possible. Researchers utilized multiple timers that began when the participants initiate movement from the starting position, and end when the participant has passed the finish line. All participants were provided with the following

standardized instructions: “I’d like you to walk 25 feet as quickly as possible, but safely. Do not slow down until you after you have passed the finish-line. Ready? Go.”

Six Minute Walk Test

The six minute walk test (6MWT) has been identified as a valid assessment of an individual’s functional capacity, accurately predicting morbidity and mortality, and better reflects activities of daily living compared to previously used assessments (92). Testing was conducted on a 60 meter marked course. During testing participants were instructed to cover the largest distance they could during the 6 minutes of allotted time. Participants walked alone during testing. The total distance covered during testing by each participant will be measured.

Body Composition

Total body and lower-limb composition was assessed using a whole body Lunar dual-energy x-ray absorptiometry (DXA) scanner (with software version 13.60.033, GE-Lunar Prodigy Advanced, Madison, WI). This test was used to compare body composition of the lower-limbs (93). Daily calibration was performed using a manufacturer produced phantom of a known density providing scan accuracy. Pre-Scan calibration quality assurance indicated a low correlation of variance (<0.2%). Subjects were asked to wear clothing without any metal pieces (ex. Zippers, buttons) and all attenuating materials and shoes were removed before testing. Subjects were positioned in the center of the DXA table in the supine position using standardized positioning; the arms close the sides of the body and with legs secured by Velcro straps. Subjects too wide for the scanning bed had each side of the body tested separately and composition of both sides of the body were added together to estimate body composition.

Assessment of the lower legs was used to determine any significant differences in lean mass of the legs between groups. From the full body scans separate regions of interest were made of the lower-legs, using the tibiofemoral joint of the knee and subtalar joint of the ankle as landmarks. The region of interest for each lower leg was quality checked by two separate researchers to ensure accuracy. Subjects had their hydration tested prior to the DXA scan. If a female subject was premenopausal, a urinary pregnancy test (SA Scientific Ltd 087525, Northalke, IL) was conducted prior the DXA scan.

Graded Exercise Test

A magnetically braked cycle ergometer (Sport Excalibur, Lode; B.V. Medical Technology, Groningen, The Netherlands) along with a metabolic cart (True One 2400, Parvo Medics, Sandy, UT) was utilized to perform a graded exercise test (GXT) to determine VO_2max and peak power output. Subjects were instructed to abstain from exercise and caffeine twelve *hr* prior to testing and to fast three to four *hr* prior to testing. A urine sample was obtained to determine urine specific gravity using a refractometer (model CLX-1, VEE GEE Scientific Inc., Kirkland, WA). Subjects were required to have a urine specific gravity between 1.004 and 1.028 to be considered adequately hydrated to perform the GXT. In the instance a participant was not adequately hydrated they were instructed to consume a glass of water and rest for 30 minutes before collecting a second sample. If at that time they were still under hydrated they were rescheduled for a subsequent day. A resting fingertip capillary blood sample was collected to determine whole blood lactate concentration prior to testing using a commercial lactate meter (Lactate Plus, Nova Biomedical, Waltham, MA) that was calibrated with known lactate standards (Lactate Plus, Lac Control Level 1, 1.0-1.6

mM) (Lactate Plus, Lac Control Level 2, 4.0-5.4 mM) before each use. Subjects were instructed to pedal at a cadence (RPM) that was comfortable and they felt they could maintain for an extended period of time. Following a one minute rest period and a five minute warm up at 50 watts (W), the GXT was initiated at a work rate (W) equal to that of the subject's body weight in kilograms (kgs) and increased in W by 50% of the subject's body weight every three minutes until the participant reaches their limit of exercise tolerance indicated by a pedal rate dropping more than 10 RPM from their self-selected cadence. At the end of each of the three-minute stages blood lactate and rating of perceived exertion (RPE) based on the Borg Scale were measured (94). Metabolic and ventilatory data were continuously measured and averaged over 30 second intervals. Heart rate (HR) was measured via a telemetric heart rate monitor (Polar T31, Polar Electro Inc., NY, USA).

VO_2max Verification

Participants were given 20 minutes of rest following the completion of the initial graded exercise test before beginning the Verification protocol (95). Using the peak power output (PPO) obtained during the initial GXT, participants performed a multistage warm-up that consisted of 2 minutes at 50% of PPO followed by 1 minute at 70% of PPO. The workload then increased to 105% of PPO and participants were instructed to maintain their self-selected cadence for as long as possible. When cadence decreased by greater than 10 rpm exercise was terminated. This protocol allowed for not allow the verification of VO_2max, but also the verification that the PPO assessed during the initial GXT would elicit VO_2max.

Individualized Graded Exercise Tests

Using the data collected from the initial GXT, subsequent GXTs were designed in a manner that allowed for participants to exercise at specific relative exercise intensities. Individualized GXTs consisted of a three minute warm-up at 25% of the PPO determined from the initial GXT and verification protocol. Following the warm-up, the work rate increased to 50% of the individuals PPO and increased by 10% every stage. Stages were three minutes in length, and at the end of each stage blood lactate and rating of perceived exertion (RPE) based on the Borg Scale were measured (94). Each individualized GXT was performed at a different cadence, and was randomly assigned prior to each visit. During the Self-Selected cadence condition subjects were instructed to pedal at the same cadence as during the initial GXT and verification protocol. During the High cadence condition participants were instructed to pedal at an rpm corresponding to 20% greater than the rpm during the Self-Selected condition. During the Low cadence condition participants were instructed to pedal at an rpm corresponding to 20% less than the rpm during the Self-Selected condition. Exercise termination was indicated by a pedal rate dropping more than 10 rpm from the predetermined rpm. Time to exhaustion (TTE) represented the amount of time exercise, not including warm-up, prior to exercise being terminated. The power output, in watts, reached (W @ TF) and the percentage of PPO (%PPO) achieved at task failure will be recorded. The percent difference in the asymmetry in contribution to total power production (% Asym) will be calculated for each exercise intensity. The following equation will be used in assessing % Asym: |% Contribution of the Left Leg - % Contribution of the Right Leg|.

Surface Electromyography (EMG)

During all GXTs bipolar surface EMG (BIOPAC® Systems, Inc., Goletta, CA) signals was collected from the left and right vastus lateralus and vastus medialus. Surface electrodes were positioned on the skin after careful shaving and cleaning of the area with an abrasive cleaner and alcohol to reduce the skin impedance. The electrodes were placed in a bipolar configuration over the belly of the muscles, parallel with the orientation of the muscle fibers and taped to the skin using micropore tape to minimize movement artifact. A reference electrode was placed over the skin of the acromion to serve as a neutral site. Raw EMG signals were smoothed with a fourth-order band-pass digital filter at 10-500 Hz. After full-wave rectification and offset correction, the onset and offset of EMG activity were determined by the signal's variation two standard deviations above the baseline value recorded between each EMG burst (96). The average root-mean-square value of three pedal strokes was calculated every 20 seconds of each stage, excluding the first and last 10 seconds of each stage.(97, 98). Offline analyses of EMG signals were developed with custom-written scripts (MATLAB 7.0, Mathworks Inc., Novi, MI, USA). For each participant and each muscle, the calculated root-mean-square values were plotted against time for each stage. The highest W that resulted in a non-significant slope coefficient for the EMG amplitude, as indicated by the root-mean-square, versus time relationship was determined to be the neuromuscular fatigue threshold (99).

Data Management and Analysis

All required documents were stored in a locked filing cabinet in the Human Performance Lab at the University of Oklahoma, and acquired data was stored on a

password protected Excel® spreadsheet on a password protected personal computer in the Human Performance Lab at the University of Oklahoma.

Statistical Analysis

All analyses was performed using IBM SPSS Statistics (version 22.0; IBM Corp., Armonk, N.Y., USA). Descriptive statistics were used to summarize the demographic data. Independent samples t-test analysis using difference scores (|left leg – right leg|) were utilized to assess differences in lower limb body composition. Due to the complex nature of both MS and bipedal movements, difference scores were also utilized for analyses to detect absolute differences without an indication of the direction of the difference. The study's current methodology of testing did not allow for the classification of limbs either as: left leg and right leg or strong leg and weak leg. Therefore, independent samples t-test were used to assess isometric strength asymmetry and walking capacity during functional performance tests. Intra class correlation coefficients (ICCs) were calculated for VO_2max and max heart rate to assess between visit reliability. Pearson's r correlations were performed to determine the relationship between physiological variables collected during the GXTs and walking capacity during functional performance tests. Spearman's correlation was ran to evaluate the relationships between EDSS scores and walking capacity. Two-way repeated measures ANOVA were used to detect group x cadence interactions for physiological variables collected during the GXTs. Differences in the contribution to total power production was assessed using a 3 way mixed factorial ANOVA with between (group) and within subject factors (cadence x intensity). When significant interactions and effects were found, Bonferroni corrections were used to determine where specific between and

within-group differences were located. An alpha level of 0.05 was the criteria to establish statistically significant differences. Cohen's d effect sizes were analyzed when appropriate. A value of < 0.19 was considered trivial, 0.20-0.49 was considered a weak effect, a value of 0.50-0.79 was considered a moderate effect, and a value of $\geq$ 0.80 was considered a strong effect (100). Effect sizes for ANOVA were analyzed when appropriate using eta-squared (η^2). A value of 0.02 was considered small effect, .13 a medium effect, and 0.26 a large effect (100, 101).

Chapter IV: Results & Discussion

Results

The results have been divided into two sections. The first section will present the statistical analysis of group data. Due to the heterogeneous nature of MS, clinical and performance decrements can be masked when examining group averages. Therefore, a second section has been added to present individual data.

Descriptive Data

A total of eighteen subjects were consented to participate in the current study. There were twelve individuals with a physician's confirmed diagnosis of MS (MS Group) and six individuals without MS (Non-MS). However, three individuals from the MS group dropped out of the study due to: time commitment issues, discomfort in the knee while cycling, and discomfort in the ankle while cycling. Therefore, fifteen individuals completed the study and were included in data analysis. Five males and four females (n = 9) were included in the MS group and three males and three females (n = 6) were included in the Non-MS group. Descriptive and anthropometric data for both groups are listed in Table 2. There were no significant between group differences ($p > 0.05$) for all descriptive and anthropometric variables. All participants in the MS group possessed a physician's diagnosis of relapse remitting MS. The Expanded Disability Status Scale (EDSS) score of 2.0 ± 2.04 indicates a minimal impairment in a neurological category. Rochester Fatigue Diaries and Modified Fatigue Impact Scale were assessed and analyzed prior to each testing session to ensure similar levels of fatigue. One visit had to be rescheduled due to increased fatigue and other MS related symptoms.

Table 2. Participant Characteristics

Variable	MS n = 9	Non-MS n = 6	*p*
Age (yrs)	46.7 ± 12.4	45.5 ± 8.96	0.84
Height (cm)	174 ± 4.66	174 ± 10.4	0.95
Body Mass (kg)	94.2 ± 17.0	80.1 ± 6.17	0.07
Body Mass Index (kg/m^2)	30.9 ± 5.79	26.7 ± 3.96	0.14
Body Fat (%)	42.6 ± 7.91	32.8 ± 14.2	0.10
Lean Mass (kg)	50.6 ± 68.9	51.8 ± 94.2	0.77
Fat Mass (kg)	38.5 ± 12.0	25.8 ± 11.9	0.07
Physical Activity (min/wk)	206.7 ± 180.3	260 ± 129.6	0.55
VO_2max (ml/kg/min)	22.4 ± 8.58	27.9 ± 10.8	0.28
Max Heart Rate (bpm)	151.8 ± 27.0	161.4 ± 24.8	0.48
EDSS	2.0 ± 2.04	N/A	N/A

Data are mean ± SD. EDSS, expanded disability status scale. *$p < 0.05$ represents a statistically significant difference across group means.

Lower-leg composition data is presented in Table 4 with gain score analysis. Results of the independent t-test indicated no significant differences between groups ($p > 0.05$) for lean mass, fat mass, and fat percentage of the lower leg.

Table 3. Gain Scores for Lean and Fat Mass of the Lower Legs

Variable	MS Δ	Non-MS Δ	*p*	d
Lean Mass (kg)	0.13 ± 0.20	0.22 ± 0.15	0.37	0.51
Fat Mass (kg)	0.08 ± 0.11	0.13 ± 0.55	0.39	1.56
Lower-Leg Fat (%)	0.00 ± 0.00	0.02 ± 0.041	0.23	5.86

Data are mean ± SD. Cohen's d = effects sizes. *$p < 0.05$ represents a statistically significant difference between groups.

Test Reliability

All GXT visits were scheduled near the same time of each day to ensure consistency across visits. Intra class correlation coefficients (ICCs) were calculated for VO_2max and max heart rate between the initial GXT and the 3 subsequent GXTs to ensure maximal effort was given during each trial. ICCs are summarized in Table 4. Both groups demonstrated strong between visit reliability for both measures indicating similar levels of effort were provided by the subjects for each test.

Table 4. Between-visit reliability of VO_2max and Max Heart Rate

	VO_2max		Max Heart Rate	
Group	ICC	CI	ICC	CI
MS	0.99	0.98 to 0.99	0.99	0.97 to 0.99
Non-MS	0.99	0.98 to 0.99	0.98	0.93 to 0.99

ICC: intraclass correlation; CI: 95% confidence limit.

Graded Exercise Tests

Physiological data collected from the three GXT conditions is presented in Table 5. The asymmetry collection and analysis software was not used during the initial GXT since the stages and work rates did not correspond to relative exercise intensities for each individual. Due to this no asymmetry data from the initial GXT is presented. Results of the two-way repeated measures ANOVA indicated no significant group x cadence interaction for TTE, W @ TF, %PPO, % Asym. However, a significant group effect for TTE ($F = 6.11$, $p = 0.028$, $\eta^2 = 0.23$) was present. Post-hoc analysis indicated that the MS group had a significantly lower TTE (mean ± SD: MS vs. Non-MS = 670.4 ± 196.6 secs vs. 869.4 ± 154.3 secs, $p = 0.028$) when collapsed across conditions.

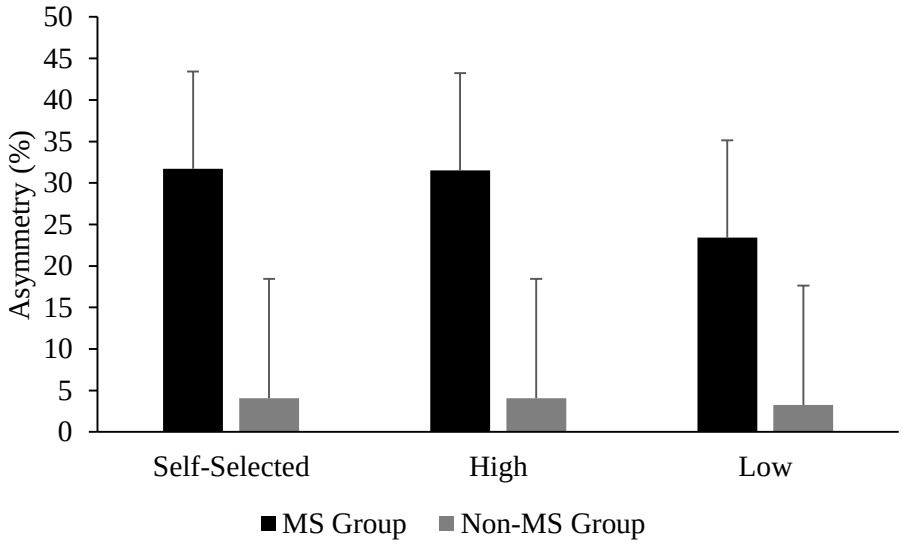
Figure 1 displays the average asymmetry between the lower limbs as a contribution to total power output during the 3 different cadence conditions (self-selected, high, and low).

Table 5. Physiological Data During GXTs

Condition	Group	TTE (secs)	W @ TF	% PPO	% Asym	Δ [La]
Self-Selected	MS	729±194	117.2±50.4	81.1±11.0	31.7±51.3	6.23±3.20
	Non-MS	889±129	151.2±65.5	88.3±9.83	4.06±2.98	6.50±3.34
	d	0.97	0.58	0.69	0.76	0.08
High	MS	564±225	103.9±49.9	71.1±16.2	31.5±38.9	6.25±3.66
	Non-MS	847±217	147.0±60.9	88.3±9.83	4.06±2.98	7.68±4.13
	d	1.28	0.47	1.28	0.70	0.37
Low	MS	716±134	116.1±42.0	83.3±7.01	23.4±38.9	5.49±3.20
	Non-MS	870±126	147.8±64.4	88.3±9.83	3.26±1.84	6.37±4.47
	d	1.18	0.58	0.59	0.73	0.22

Data are mean ± SD. Cohen's d: effect sizes; TTE: Time to Exhaustion; W @ TF: Watts at Task Failure; % PPO: Percent of Peak Power Output; % Asym: Percent difference between limbs in power production contribution.

Figure 1. Average Lower Leg Asymmetry in Contribution to Power Production



Data are presented as mean ± SE. *$p < 0.05$ represents a statistically significant difference.

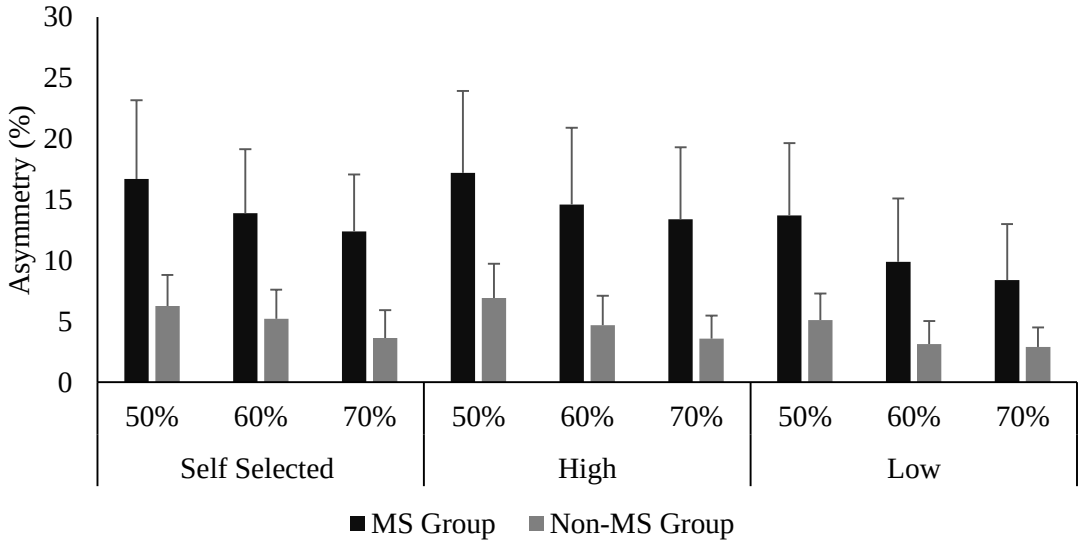
Absolute differences in the contribution to total power production at 50, 60, and 70% of PPO are described in Table 6 and illustrated in Figure 2. These submaximal intensities represent the intensities that all subjects were able to complete before task failure. A 3 way mixed factorial ANOVA with between and within subject factors revealed no statistically significant group x cadence x intensity interaction ($F = 0.211$, $p = 0.925$, $\eta^2 = 0.95$). No two way interactions were present ($p>0.05$). No significant main effects were present for group, cadence, or intensity ($p >0.05$).

Table 6. Percent Difference in Contribution to Power Production at 50, 60, and 70% Peak Power Output

Condition	Group	50 % PPO	60% PPO	70% PPO
Self-Selected	MS	16.7 ± 17.1	13.9 ± 15.3	12.4 ± 12.1
	Non-MS	6.26 ± 5.37	5.21 ± 4.08	3.63 ± 3.93
	d	0.82	0.78	0.97
High	MS	17.2 ± 15.3	14.6 ± 11.6	13.4 ± 12.0
	Non-MS	6.94 ± 3.57	4.70 ± 4.47	3.59 ± 2.58
	d	0.92	1.13	1.13
Low	MS	13.7 ± 13.1	9.90 ± 10.9	8.41 ± 9.40
	Non-MS	5.10 ± 2.99	3.13 ± 2.89	2.91 ± 3.07
	d	0.91	0.85	0.79

Data are mean ± SD. d: effect sizes; 50 % PPO: 50 percent of peak power output; 60 % PPO: 60 percent of peak power output; 70 % PPO: 70 percent of peak power output. *$p < 0.05$ represents a statistically significant difference between groups. †$p < 0.05$ represents a statistically significant difference from High. ǂ$p < 0.05$ represents a statistically significant difference from Low.

Figure 2. Percent Difference in Contribution to Power Production at 50, 60, and 70% Peak Power Output

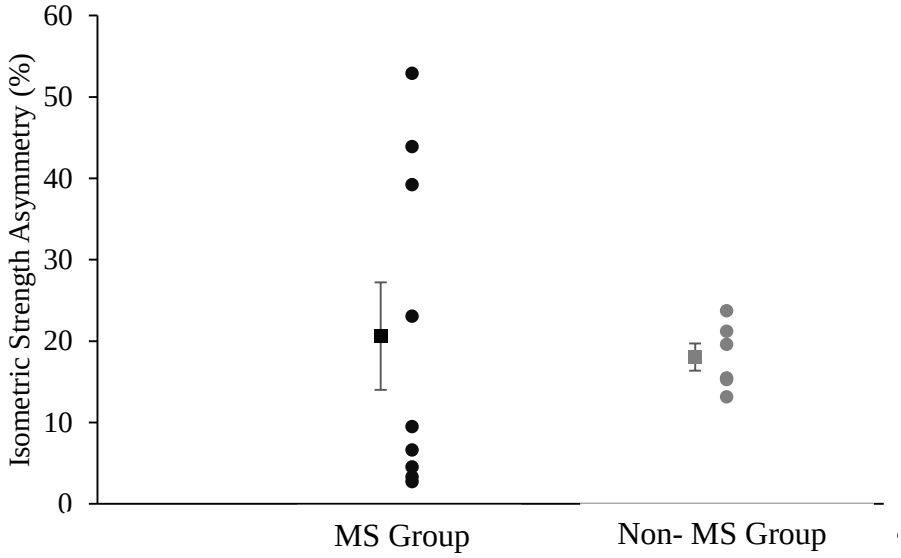


Data are mean ± SE. 50%: 50 percent of peak power output; 60%: 60 percent of peak power output; 70%: 70 percent of peak power output. *$p < 0.05$ represents a statistically significant difference between groups. †$p < 0.05$ represents a statistically significant difference from High. ǂ$p < 0.05$ represents a statistically significant difference from Low.

Maximal Voluntary Contractions

The group and individual isometric strength asymmetry results are illustrated in Figure 3. Independent t-tests indicated there was no significant differences between groups for the strength asymmetry score (mean ± SD: MS group vs. Non-MS group = 20.6 ± 19.8 vs. 18.0 ± 4.09, p = 0.76, d = 0.18).

Figure 3. Isometric Strength Asymmetry

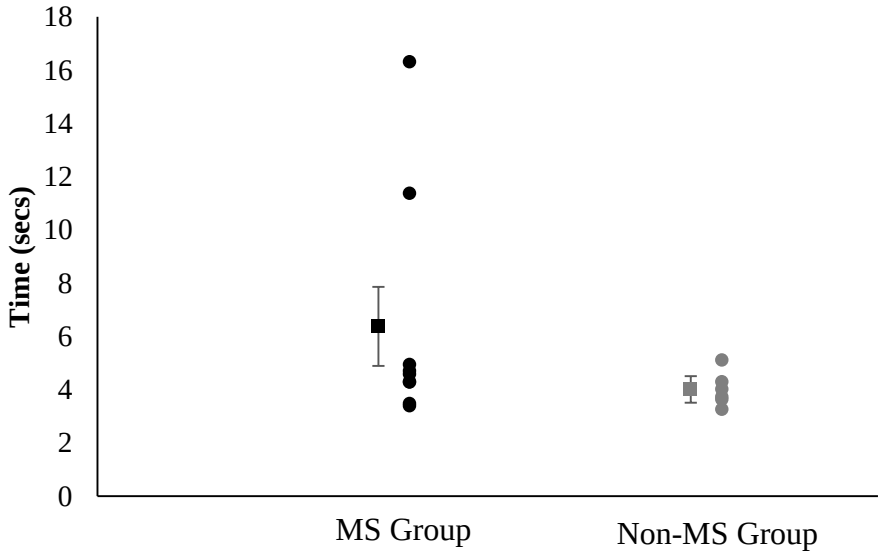


Data are presented as mean ± SE. *$p < 0.05$ represents a statistically significant difference.

Functional Performance Tests

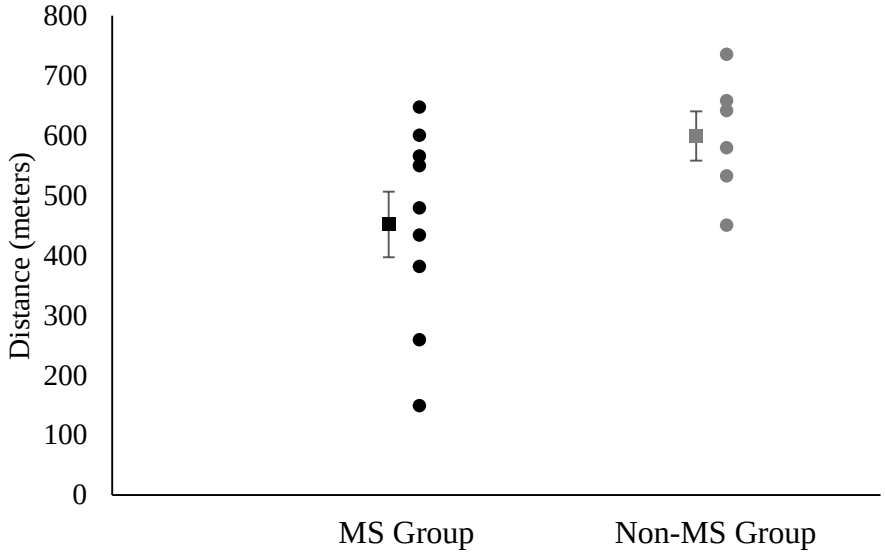
The group and individual results of the functional performance tests are presented in Figures 4 and 5. Independent t-tests indicated no statistically significant differences between groups for either the 25WT (mean ± SD: MS group vs. Non-MS group = 6.37 ± 4.44 vs. 4.01 ± 0.64, p = 0.23, d = 0.75) or 6MWT (mean ± SD: MS group vs. Non-MS group = 451.6 ± 164.9 vs. 599.4 ± 100.9, p = 0.73, d = 1.08).

Figure 4. 25WT Performance



Data are presented as mean ± SE. *$p < 0.05$ represents a statistically significant difference

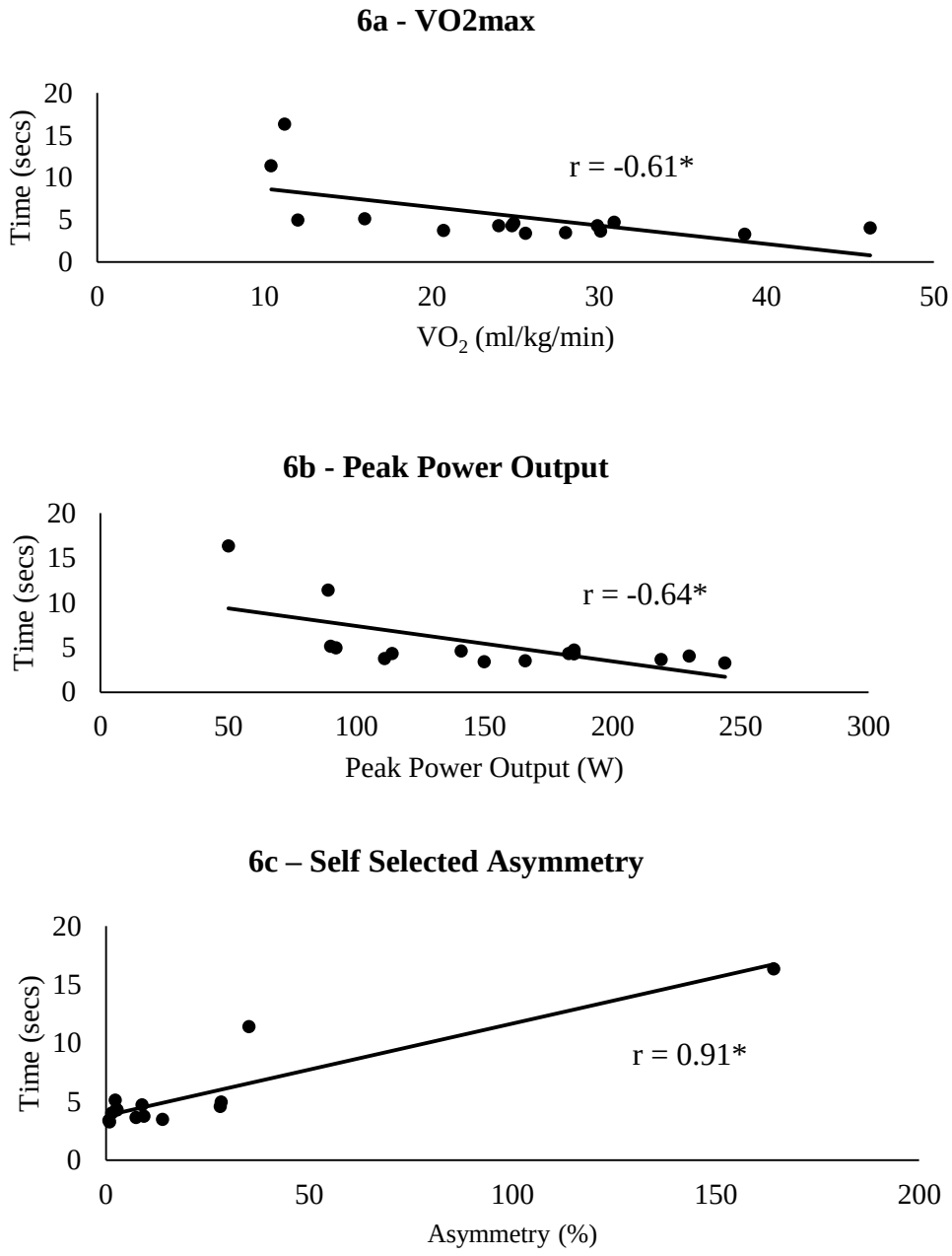
Figure 5. 6MWT Performance



Data are presented as mean ± SE. *$p < 0.05$ represents a statistically significant difference

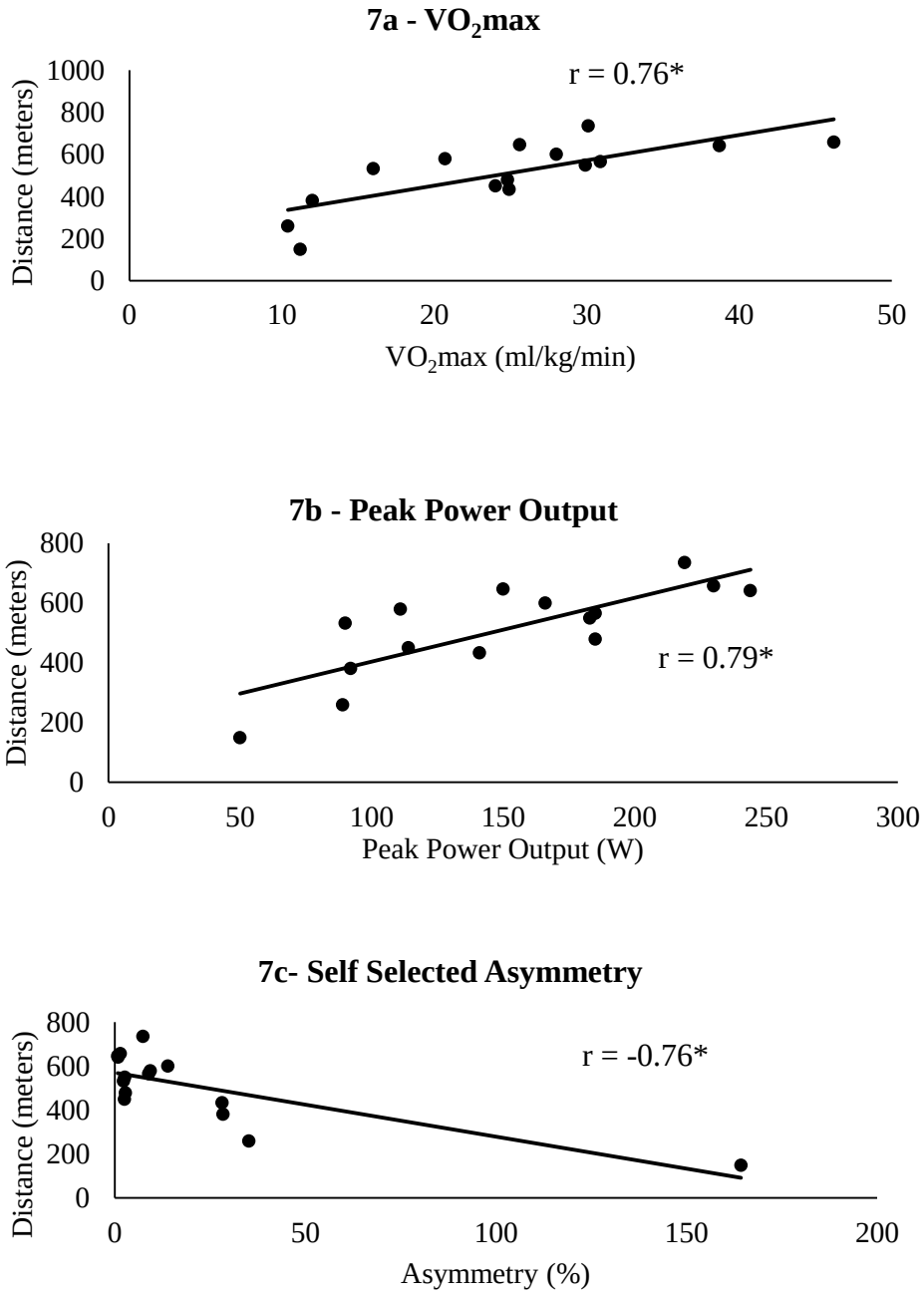
Correlations

Figure 6. Correlation between Physiological Variables and 25WT Performance in Both Groups (n = 15)



*p<0.05 represent statistically significant correlation

Figure 7. Correlation Coefficients between Physiological variables and 6MWT Performance in Both Groups (n = 15)



*p<0.05 represent statistically significant correlation

Pearson's correlations were measured to assess the relationship between functional performance tests, 25WT and 6MWT, and the physiological variables assessed as such: strength asymmetry score, VO_2max, PPO, and Asymmetry during the Self-Selected GXT (Asym. Self-Selected). The Asymmetry during the Self-Selected GXT was the only asymmetry condition correlated to walking capacity assessed via the functional performance variables since these tests were performed at a self-selected speed. The results for all 15 pooled subjects are presented in Table 8. There was a significant correlation between VO_2max, PPO, and Asym. Self-Selected for both the 25WT and 6MWT. These are illustrated in Figures 6 and 7.

Table 7. Correlation Coefficients for the Relationship between Physiological Variables and Functional Performance Tests

Pooled Subjects (n = 15)								
	Strength Asymmetry		VO_2max		PPO		Asym. Self Selected	
Test	r	*p*	r	*p*	r	*p*	r	*p*
25WT (secs)	0.34	0.15	-0.61	0.02*	-0.64	0.01*	0.91	<0.001*
6MWT (meters)	-0.33	0.23	0.76	<0.001*	0.79	<0.001*	-0.76	<0.001*

Data are Pearson's r correlation coefficients. 25 foot walk test; 6MW: 6 minute walk test; VO_2max: maximal oxygen consumption; PPO: peak power output; Asym. Self-Selected: asymmetry in present contribution to total power output during self-selected graded exercise test. *$p < 0.05$ represents a statistically significant correlation.

Groups were separated to investigate the relationships present in each group. In the MS group (Table 8) significant correlations were present between 25WT and VO_2max ($r = 0.75$ and $p = 0.006$), PPO ($r = 0.82$ and $p = 0.006$), and Asym. Self-Selected ($r = 0.91$ and $p = <0.001$). Significant correlations were also present between 6MWT and VO_2max ($r = 0.87$ and $p = 0.002$), PPO ($r = 0.87$ and $p = 0.002$), and Asym. Self-Selected ($r = 0.82$ and $p = 0.006$). In the Non-MS group (Table 9) there was only a significant correlation between PPO and 6MWT ($r = 0.76$, $p = 0.04$)

Table 8. Correlation Coefficients for the Relationship between Physiological Variables and Functional Performance Tests in MS

	MS (n = 9)							
	Strength Asymmetry		VO_2max		PPO		Asym. Self-Selected	
Test	r	*p*	r	*p*	r	*p*	R	*p*
25WT (secs)	0.40	0.28	-0.75	0.02*	-0.82	0.006*	0.91	<0.001*
6MWT (meters)	-0.38	0.32	0.87	0.002*	0.87	0.002*	-0.82	0.006*

Data are Pearson's r correlation coefficients. 25 foot walk test; 6MW: 6 minute walk test; VO_2max: maximal oxygen consumption; PPO: peak power output; Asym. Self-Selected: asymmetry in percent contribution to total power output during self-selected graded exercise test. *$p < 0.05$ represents a statistically significant correlation

Table 9. Correlation Coefficients for the Relationship between Physiological Variables and Functional Performance Tests in Non-MS Group

Non- MS (n = 6)								
	Strength Asymmetry		VO_2max		PPO		Asym. Self Selected	
Test	r	*p*	r	*p*	r	*p*	R	*p*
25WT (secs)	0.17	0.71	-0.48	0.28	-0.62	0.14	-0.079	0.87
6WT (meters)	-0.13	0.78	0.54	0.21	0.76	0.04*	0.14	0.76

Data are Pearson's r correlation coefficients. 25 foot walk test; 6MW: 6 minute walk test; VO_2max: maximal oxygen consumption; PPO: peak power output; Asym. Self-Selected: asymmetry in present contribution to total power output during self-selected graded exercise test.
*$p < 0.05$ represents a statistically significant correlation

Additionally, Pearson's correlations were measured to assess the relationship between EDSS score and the percent difference between the lower limbs in contribution to total power output during the Self-Selected, High, and Low cadence conditions in the MS group. Results are described in Table 10, and displayed in Figure 8. A significant correlation was present between EDSS score and percent asymmetry in the Self-Selected ($r = 0.78$ and $p = 0.01$), High ($r = 0.839$ and $p = 0.004$), and Low ($r = 0.78$ and $p = 0.01$) cadence conditions.

Table 10. Correlation Coefficients for the Relationship between Expanded Disability Status Score and Asymmetry

MS (n = 9)						
	Asym. Self-Selected		Asym. High		Asym. Low	
Variable	r	*p*	r	*p*	r	*p*
EDSS	0.79	0.01*	0.82	0.004*	0.76	0.01*

Data are Pearson's r correlation coefficients. EDSS: Expanded Disability Status Score; Asym. Self-Selected: asymmetry in percent contribution to total power output during self-selected cadence graded exercise test; Asym. High: asymmetry in percent contribution to total power output during high cadence graded exercise test; Asym. Low: asymmetry in percent contribution to total power output during low cadence graded exercise test. *$p < 0.05$ represents a statistically significant correlation

Figure 8. Correlation Coefficients between Expanded Disability Status Scale Score and Asymmetry in MS Group (n = 9)

Figure 8a. Self-Selected Cadence

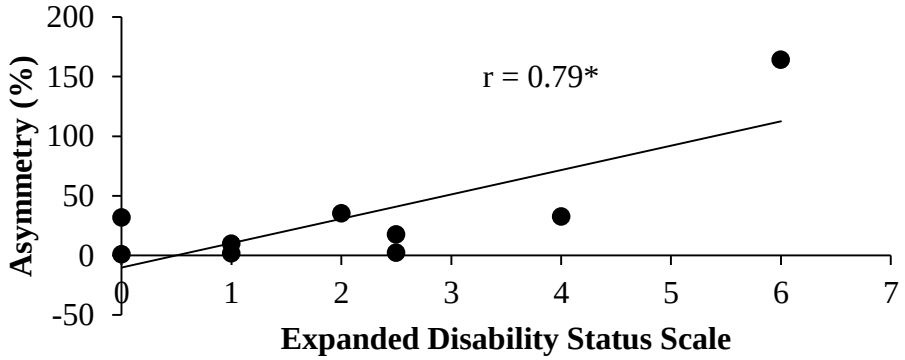


Figure 8b. High Cadence

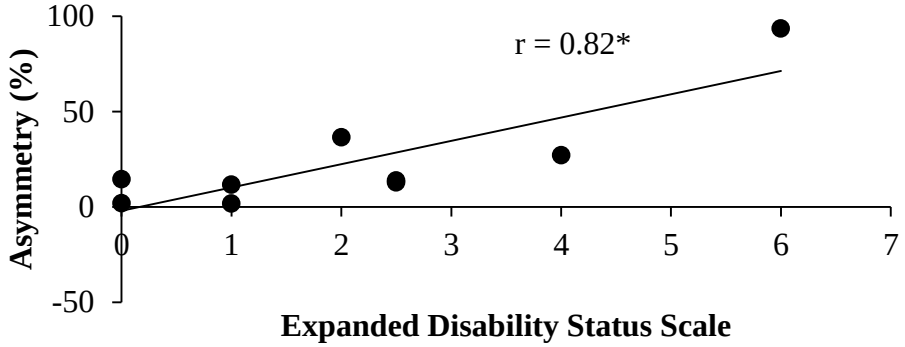
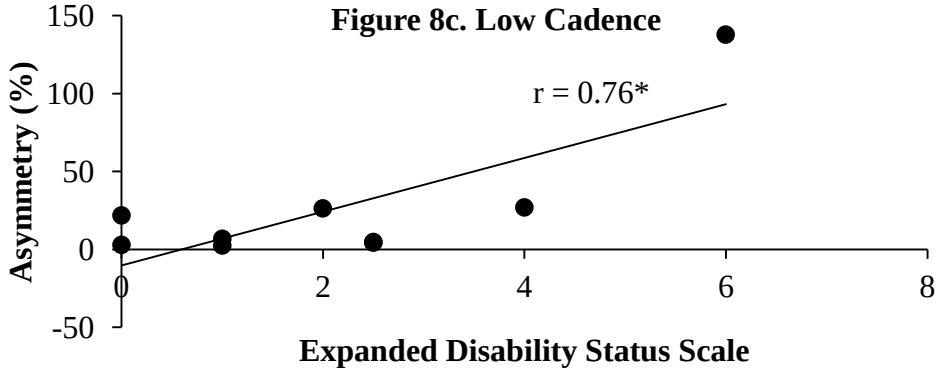


Figure 8c. Low Cadence



*p<0.05 represent statistically significant correlation

Electromyography

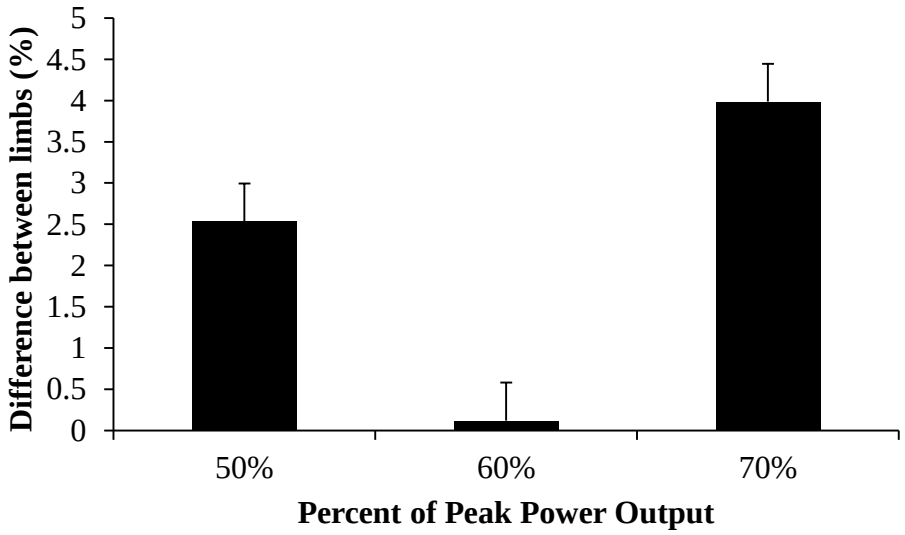
Due to issues encountered during data collection, a sufficient sample size was not able to be obtained to perform the original analysis intended for the EMG data. However, the RMS amplitude across a relative exercise intensity was examined as a percentage of the max RMS amplitude obtained during the test. The percent difference between the lower limbs for the percentage of max RMS reached during each exercise intensity was calculated and displayed in Figures 9, 10, and 11. A one way repeated measures ANOVA was performed to detect any significant difference between exercise intensities within each cadence condition. No significant differences were present between intensities within each condition ($p>0.05$). The absolute value of the normalized RMS amplitude is presented in Table 12. Two-way repeated measures ANOVA were used to limb x exercise intensity interactions. No significant differences were present ($p>0.05$). Additionally, the average RMS amplitude for each leg during each exercise intensity was plotted against time. Two-way repeated measures ANOVA were used to limb x exercise intensity interactions. Data is presented in Table 13. No significant differences were present ($p>0.05$).

Table 11. Percent Difference between Lower Limbs in Percentage of Max RMS Reached for 50, 60, and 70% Peak Power Output

Condition	50 % PPO	60% PPO	70% PPO
Self-Selected	2.53 ± 3.79	0.12 ± 0.02	3.97 ± 5.41
High	5.43 ± 6.29	5.54 ± 4.61	2.38 ± 6.08
Low	7.50 ± 6.75	6.76 ± 9.25	2.95 ± 9.87

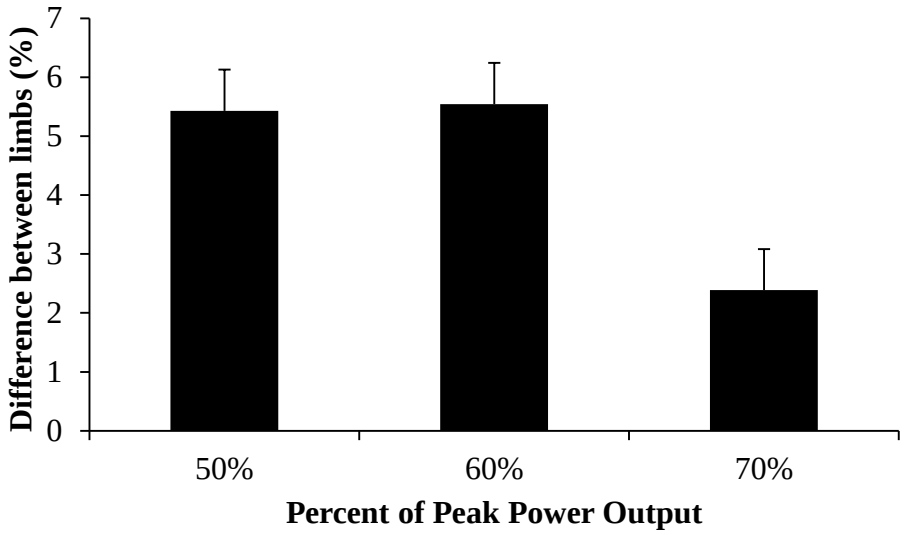
50%: 50 percent of peak power output; 60%: 60 percent of peak power output; 70%: 70 percent of peak power output.

Figure 9. RMS Amplitude during Self-Selected Cadence



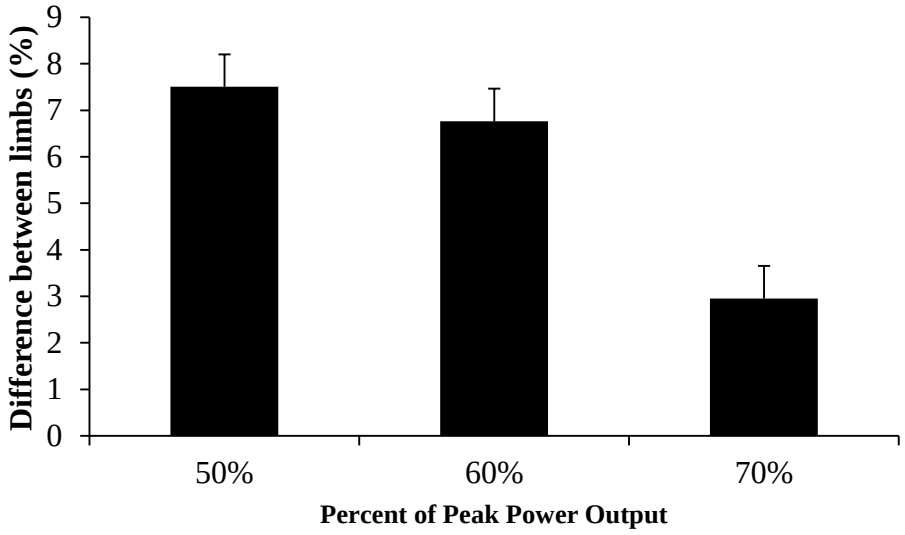
Data are presented as mean ± SE. 50%: 50 percent of peak power output; 60%: 60 percent of peak power output; 70%: 70 percent of peak power output. *$p < 0.05$ represents a statistically significant difference.

Figure 10. RMS Amplitude during High Cadence



Data are presented as mean ± SE. 50%: 50 percent of peak power output; 60%: 60 percent of peak power output; 70%: 70 percent of peak power output. *$p < 0.05$ represents a statistically significant difference

Figure 11. RMS Amplitude during Low Cadence



Data are presented as mean ± SE. 50%: 50 percent of peak power output; 60%: 60 percent of peak power output; 70%: 70 percent of peak power output. *$p < 0.05$ represents a statistically significant difference

Table 12. Average Slope Coefficients of RMS Amplitude.

	50%		60%		70%	
Condition	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg
Self-Selected	0.001±0.001	0.001±0.001	0.001±0.001	0.001±0.001	-0.004 ±0.001	0.001±0.001
High	-0.001±0.001	0.001±0.001	-0.001±0.001	-0.003±0.002	0.001 ± 0.001	0.002±0.001
Low	0.001±0.001	0.001±0.001	0.001±0.001	-0.001±0.001	0.001 ± 0.001	0.001±0.001

50%: 50 percent of peak power output; 60%: 60 percent of peak power output; 70%: 70 percent of peak power output.

Table 13. Absolute RMS Amplitude

	50%		60%		70%	
Condition	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg
Self-Selected	63.9 ± 2.53	61.4 ± 3.79	72.7 ± 0.11	72.8 ± 0.02	85.7 ± 3.98	81.7 ± 5.40
High	74.1 ± 5.43	79.5 ± 6.28	81.2 ± 5.54	86.8 ± 4.61	93.4 ± 2.39	95.8 ± 6.08
Low	59.5 ± 7.51	67.03 ± 6.76	72.1 ± 6.76	78.9 ± 9.25	87.9 ± 2.95	90.9 ± 9.87

50%: 50 percent of peak power output; 60%: 60 percent of peak power output; 70%: 70 percent of peak power output.

Individual Data

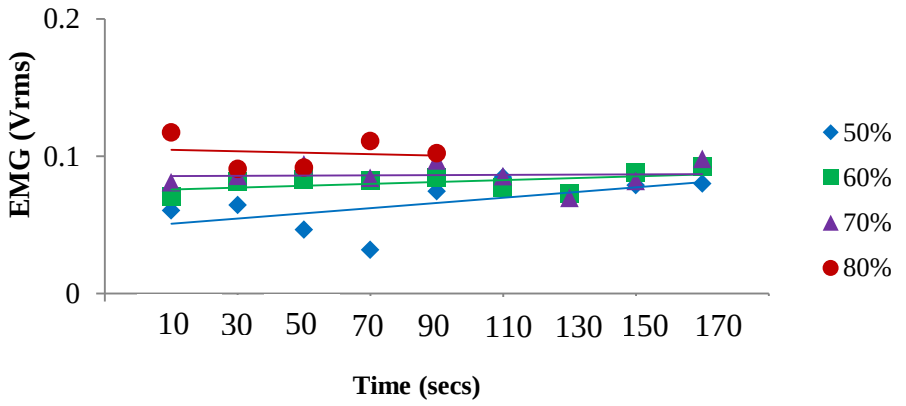
Due to the heterogeneous nature of MS, clinical and performance decrements can be masked when examining group averages. For this reason we have chosen to dedicate this next section to presenting a sample of individual data that is representative of the MS group averages and an individual that does not follow the trends of the group.

Electromyography

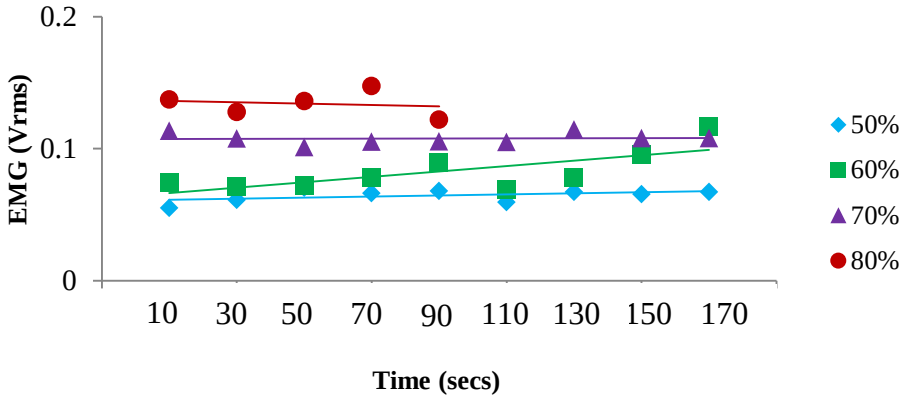
The following data is presented as individual data, and not as group means. Due to complications with methodology during data collection, a sufficient data set was not obtained that allowed for statistical analysis in the manner that was originally intended for the EMG data. EMG was collected throughout each of the GXTs on the Vastus Medialus and Vastus Lateralus. The RMS sample was obtained for each muscle during each stage every 20 seconds (the first 10 secs and last 10 secs were excluded from analysis) and graphed against time. The neuromuscular fatigue threshold would be determined as the highest power output to that resulted in a non-significant slope coefficient for the EMG amplitude. Figures 12a. and 12b. are examples of the intended method for analysis.

Figure 12. RMS Slope during GXT

12a. Right Vastus Medialis MS Subject



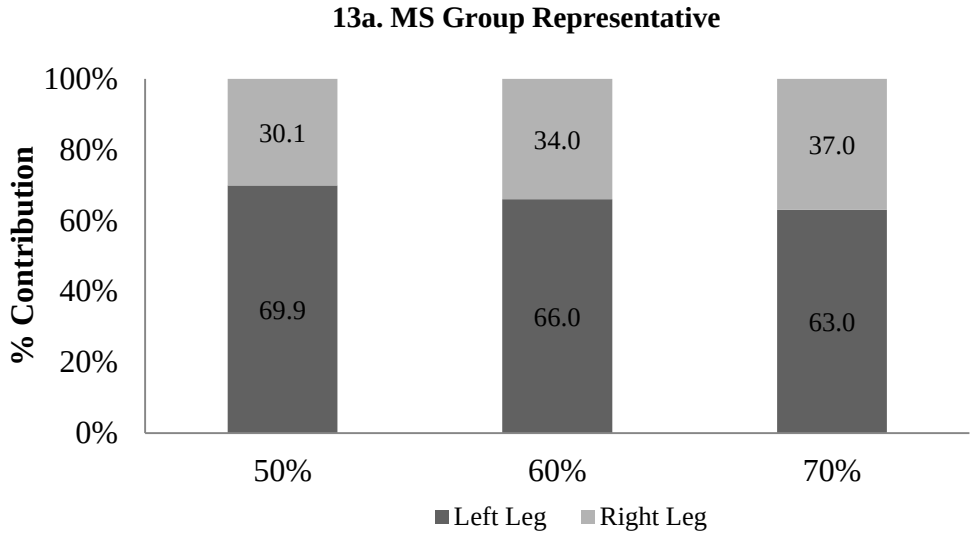
12b. Left Vastus Medialis MS Subject



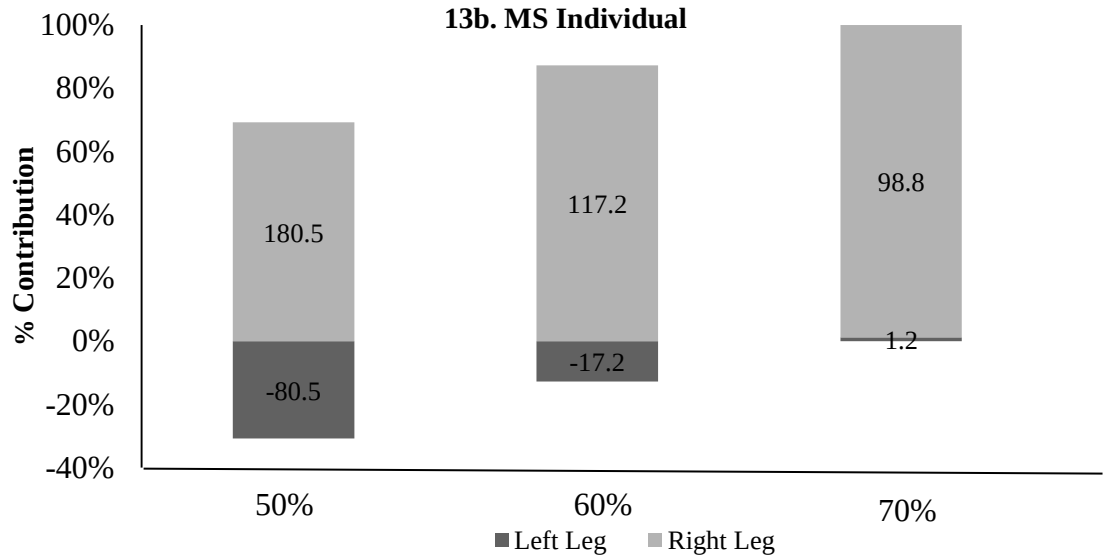
Power Output Asymmetry

The intensities illustrated for each figure indicated the highest intensity completed prior to task failure for each cadence condition. Figures 13a, 14a, and 15a illustrate an average representation for the MS group for the Self-Selected, High, and Low cadences. Figures 13b, 14b, and 15b illustrate individual data for each cadence condition. It should be noted that the individual presented possessed an EDSS of 6 while the MS group average was 2.0 ± 2.04.

Figure 13. Percent Contribution during Self-Selected Cadence GXT

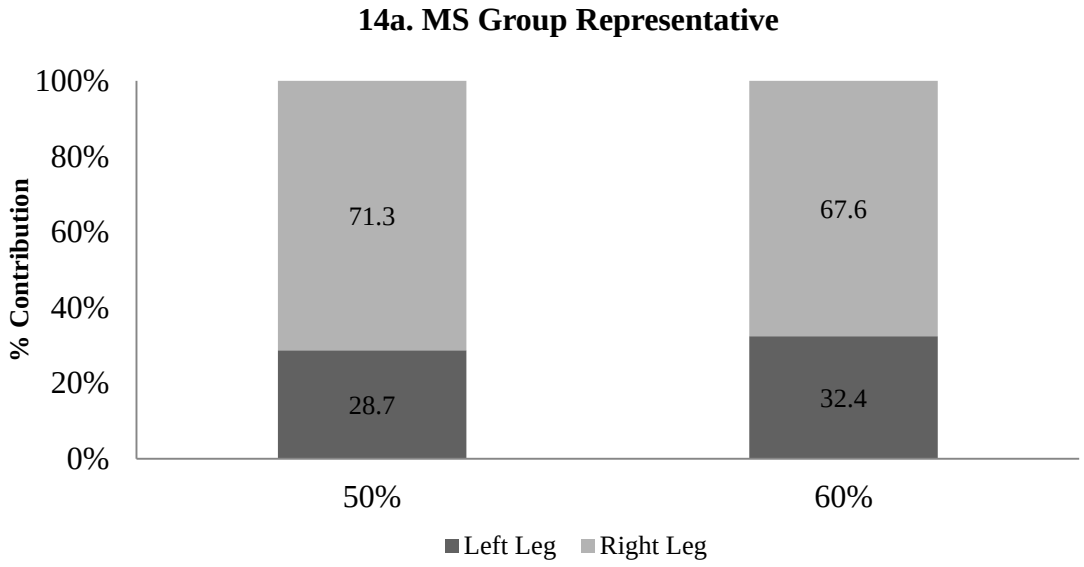


50%: 50 percent of peak power output; 60%: 60 percent of peak power output; 70%: 70 percent of peak power output.

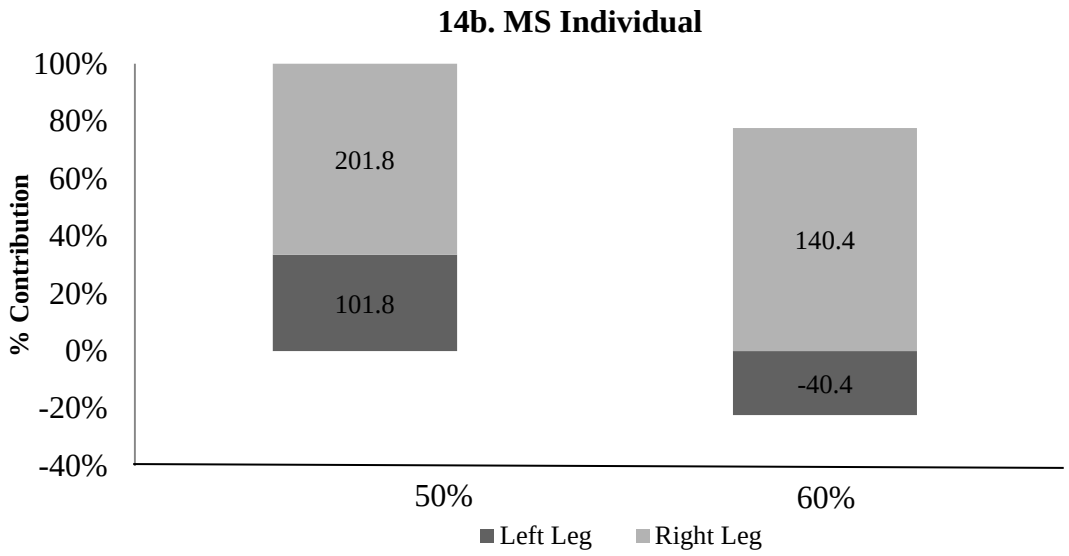


50%: 50 percent of peak power output; 60%: 60 percent of peak power output; 70%: 70 percent of peak power output.

Figure 14. Percent Contribution during High Cadence GXT

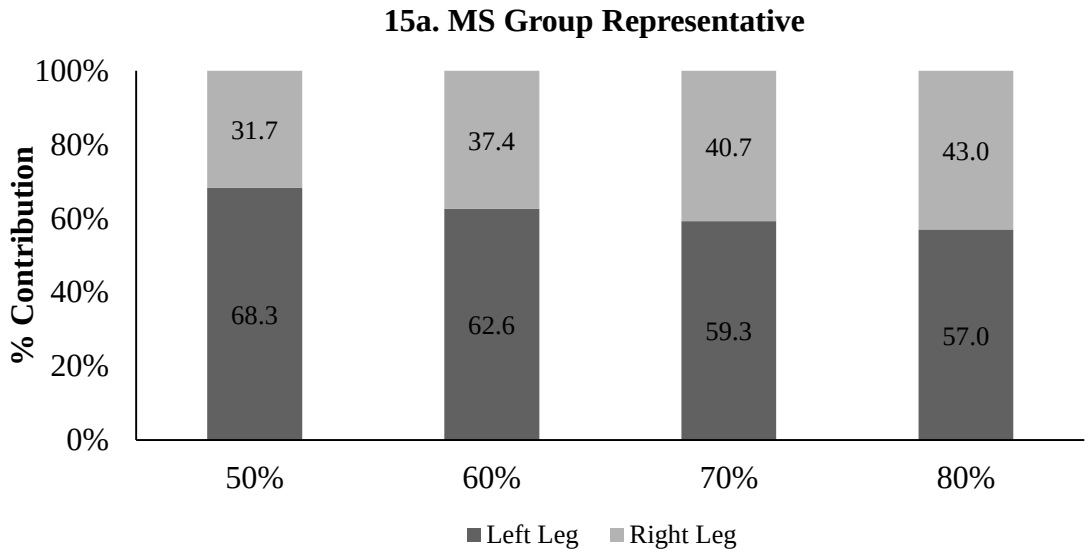


50%: 50 percent of peak power output; 60%: 60 percent of peak power output.

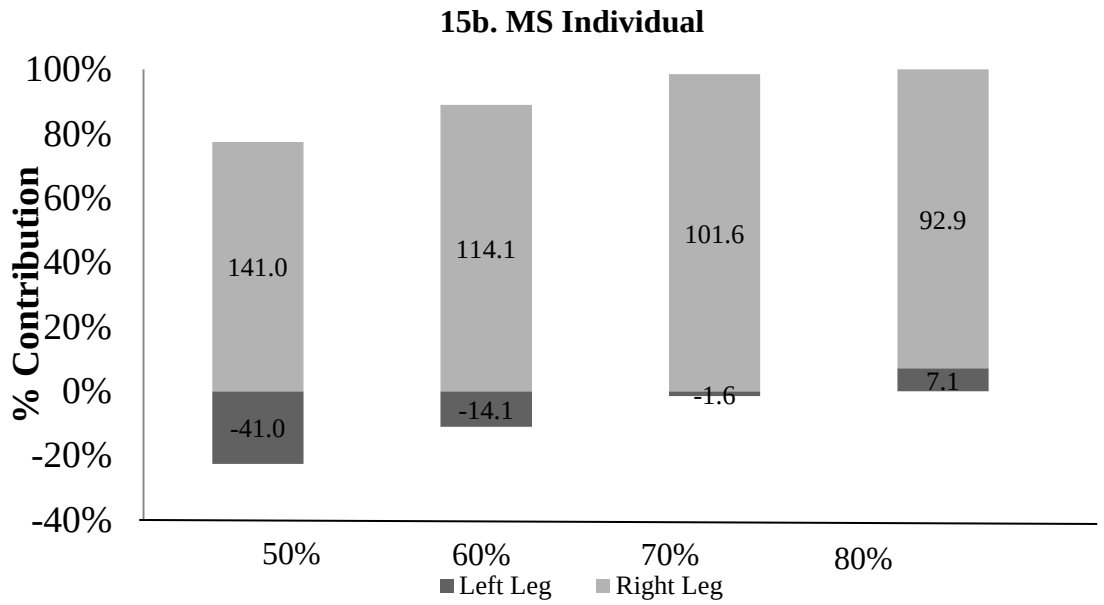


50%: 50 percent of peak power output; 60%: 60 percent of peak power output.

Figure 15. Percent Contribution during Low Cadence GXT



50%: 50 percent of peak power output; 60%: 60 percent of peak power output. 70%: 70 percent of peak power output. 80%: 80 percent of peak power output.



50%: 50 percent of peak power output; 60%: 60 percent of peak power output. 70%: 70 percent of peak power output. 80%: 80 percent of peak power output.

Discussion

The following paragraphs will discuss in detail the main findings of the study and how the results compare or contrast with previous literature. It will conclude with a paragraph addressing limitations associated with the study and considerations for future research directions.

Main Findings

1. No statistically significant differences between groups were present for W @ TF, %PPO, and % Asym. across all three cadence conditions (Self-Selected, High, and Low).
2. A statistically significant group effect was present for TTE during GXTs with the MS group reaching exhaustion quicker than the Non-MS group.
3. A statistically significant interaction between group, cadence, and exercise intensity was not detected with no main effects present as well.
4. The % asymmetry score for MVCs was not statistically significant between groups.
5. Performance on 25WT and 6MWT was not statistically different between groups.
6. VO2max, PPO, and Asym. Self-Selected were significantly correlated with performance on both the 25WT and 6MT when subjects are pooled.
7. In the Non-MS group only a significant correlation between PPO and performance on the 6MW was present.
8. In the MS group VO2max, PPO, and Asym. Self-Selected were significantly correlated with performance during both the 25WT and 6MWT.

The current study was conducted with the purpose of investigating several facets pertaining to bilateral asymmetry in persons with MS. First, we sought to investigate whether persons with MS exhibit greater bilateral asymmetry in power production contribution during a double leg graded exercise test compared to healthy controls. Second, we sought to examine bilateral differences in muscle activation of the vastus lateralus and vastus medialus during a double leg cycling GXT. Third, we sought to investigate how exercise intensity and cadence selection affect the manifestation of bilateral asymmetry in persons with MS during a graded exercise test. Fourth, we sought to investigate bilateral asymmetry in isometric strength of the knee extensors.

We hypothesized that bilateral asymmetry, in regards to power production contribution, during a double leg graded exercise test would be significantly greater in persons with MS compared to healthy controls. Results from the current study indicate that no statistically significant differences in bilateral asymmetry for power production contribution during a double leg GXT were present between the MS group and Non-MS group; therefore this hypothesis was rejected. We hypothesized that a bilateral difference in muscle activation in the vastus lateralis and vastus medialis would be present in the MS group during a double leg graded exercise test. Due to complications during data collection an appropriate data set to answer this question could not be obtained thus this question cannot be fully addressed in the current study. However, individual data relating to this question will be discussed later in this chapter. We hypothesized that exercise intensity and alterations to cadence would have a significant effect on the level of bilateral asymmetry in power production contribution. Results from the current study indicate that exercise intensity and cadence do not have a

statistically significant effect on bilateral asymmetry in power production contribution. We hypothesized that persons with MS would exhibit greater bilateral asymmetry in isometric strength of the knee extensors. The results of the current study indicate that the MS group does not have a statistically significant difference in strength asymmetry score for isometric knee extensor strength from the Non-MS group.

Bilateral Asymmetry

Previous literature has shown evidence of bilateral asymmetry in individual's with MS (4-8). More specifically, bilateral asymmetries have been reported in persons with MS for VO_2max, PPO, and work performed during single leg cycling (4, 5, 8). One of the earliest reports of asymmetry is seen in a case study in which White et al. observed that during single leg cycling the right limb was able to achieve a PPO of 170W while the left leg was only able to achieve a PPO of 150W (8). These single leg PPOs translated to 85% and 75%, respectively, of double leg PPO resulting in a 10% difference in performance between limbs. Larson et al. reported a 17.1W difference between limbs during a single leg ramp incremental exercise test indicating a 28.0% difference in PPO between the strong and weak legs in the MS group compared to the 4.3% in the healthy control group (4). A 22.6% difference in VO_2peak achieved between single leg trails was only observed for the MS group with only a 5% difference observed in the healthy control group. Bilateral asymmetry in work performed during single leg cycling at a fixed submaximal workload was also observed in an MS cohort by Larson et al. (5). Persons with MS had a statistically significant between-leg difference for work performed during the single leg trial. This between leg difference was also statistically greater compared to between limb differences in healthy controls.

To this point all of the previous studies examining asymmetries in lower limb performance during cycling in persons with MS have utilized single leg cycling. Essentially these previous studies have required individuals to perform a bipedal movement in a uniped manner. By completely isolating the limbs during this exercise modality, researchers may have altered the natural biomechanics of the cycling modality which in part could explain the different findings between the current study and previous literature The uniqueness of the current study is that the methodology allows for the observation of the interaction of the lower limbs during a bipedal movement when bilateral asymmetry may be present. In addition, the current study is one of the first to use dual power meter equipment in the study methodology with the primary purpose of observing bilateral differences in the contribution of each leg to total power production at relative exercise intensities in an MS cohort. The utilization of this methodology allows for the current study to be one of the first to observe in an MS cohort the limbs performing in a dependent manner with each other rather than independently.

The current study observed no statistically significant differences in percent difference in the contribution to power production between the limbs across three relative exercise intensities (50, 60, and 70% of PPO). However, asymmetry ranged from 8.41 to17.2% in the MS group with effect sizes ranging from 0.79 to 1.13, indicative of a moderate to strong effect. Although not statistically different, a moderate to strong effect for asymmetry is present between the groups suggesting that larger levels of asymmetry may be present in the MS group. The non-significant findings of the current study are not in agreement with previous literature pertaining to bilateral

asymmetry during cycling in persons with MS (4, 5, 8). This discrepancy may be due to methodological differences between the current study and previous ones. As mentioned earlier, previous studies have utilized single leg cycling while the current study utilized double leg cycling (4, 5, 8). Both White et al. and Larson et al. assessed bilateral asymmetry in a similar manner; both used a ramp GXT protocol and were only able to assess bilateral asymmetry at PPO and not submaximal intensities (4, 8). The magnitude of asymmetry seen in the current study (range 8.41 to 17.2%) was similar to White et al. (10%) but lower than Larson et al. (28%). However, Larson et al. reported an effect size of 1.7, indicating a strong effect, for bilateral leg differences in PPO between groups. Similar effect sizes are present in both Larson et al. and the current study but with differences in significant and non-significant findings suggest that differences in subject pools could potentially play a role. It also suggests that similar findings for the presence of asymmetry may be present but cannot be detected with the current sample size and statistical analysis.

Differences between the current study and previous literature regarding the exercise intensity and exercise intensity domain in which bilateral asymmetry was assessed could provide insight into the discrepancies in findings. Exercise intensity and the exercise intensity domain in which exercise is performed at has an impact on the rate and nature of fatigue development during exercise. The upper limit of the moderate exercise intensity domain is indicated by the lactate threshold, and the boundary between he heavy and severe exercise intensity domains is indicated by the critical power, the highest metabolic rate that can be maintained for an extended period of time. Exercise in the severe exercise intensity domain is associated with elevated motor unit

recruitment and a disproportionate increase in the rate of neuromuscular fatigue development compared to lower exercise intensities (102, 103). This increased rate of neuromuscular fatigue development can be linked with reductions in muscle excitability due to alterations in plasma potassium [K^+], which may reflect a rise in interstitial [K^+] within the t-tubule which weakens the propagation of action potentials along the surface of the membrane, resulting in a reduced amplitude of the action potentials (104, 105). This process attenuates Ca^{2+} release from the sarcoplasmic reticulum, reducing cross-bridge formation and the force-generating capacity of the myocyte which further contributes to fatigue (106).. By assessing differences in power production between limbs at PPO, this would have allowed for participants to exercise in the severe exercise intensity domain and induce alterations to the excitability of the myocytes. Persons with MS already experience weakening or inhibition of action potentials from the central nervous system (CNS) through the neuromuscular junction, coupled with the further reduction in the propagation of action potential along the myocyte membrane could have induced the bilateral asymmetry reported by Larson et al. and White et al. (4, 8, 88). Assessment of bilateral asymmetry at peak power output was not done in the current study due to methodological differences. However, similar findings have been found in unpublished pilot data from the current laboratory when examining bilateral differences in power output at the gas exchange threshold, critical power, and PPO in persons with MS. No significant differences between limbs were present except at PPO.

Participants in the current study completed an initial GXT to determine VO_2max and PPO. Subsequent GXTs were individualized in a manner that allowed subjects to exercise at relative exercise intensities from 50 to 100% of PPO. Individualized GXTs

consisted of a 3 minute warm-up at 25% of PPO and then immediately transitioned into 3 minute stages at relative exercise intensities from 50 to 100% or their PPO in succession. ICCs were conducted for VO_2max (MS group: 0.99; Non-MS group: 0.99) and max heart rate (MS group: 0.99; Non-MS group: 0.98) obtained from each GXT, and indicated a strong reliability between visits for both measures. It was our intention to assess bilateral asymmetry from 50 to 100% of PPO. However, we were only able to obtain a complete data set for analysis for 50 to 70% of PPO due to subjects reaching task failure much earlier than anticipated. Although similar warmup intensities and length compared to the current study were utilized in previous literature, differences in the increase in work rate and length of test do exist. Larson et al. allotted participants a 5 minute rest upon completion of the warmup before beginning a ramp protocol corresponding to a 1W increase every 2 secs while White et al. started at 100W and increased 10W per minute (4, 8). Upon completion of the 70% stage in the current study subjects had been exercising continuously for 720 secs while single leg GXTs were completed in 147 secs and 113 secs in Larson et al. and 300 and 420 secs in White et al (4, 8). Differences in the increase in work-rate between the current study and previous ones resulted in drastically different exercise time. The length of the exercise protocol begins to plays a factor in the development of fatigue, especially when exercising above lactate threshold (LT) (107). Lactate threshold has been reported to occur between 50 and 65% of VO2max in healthy adults and ~57% in those with MS (108, 109). We speculate that the current methodology required participants to exercise for several minutes at or above their lactate threshold, inducing a metabolic response resulting in the accumulation of metabolic by products such as lactate and H^+, as evidenced by an

increase of 5.49 to 7.68 mmol/l in blood [La]. The accumulation of lactate is due to an imbalance between its rate of production and its rate of removal. Training status plays a large role in the ability to maintain this balance, with those possessing higher levels of endurance training demonstrating greater abilities either remove or reduce the production of lactate (107). Participants in the current study were considered sedentary, indicating lower levels of lactate kinetics. A strong correlation exists between increases in lactate concentration and reductions in power output (110). This accumulation of lactate coupled with an extended exercise time at or above lactate threshold could potentially have induced the development of peripheral fatigue resulting in the termination of exercise prior to reaching the severe exercise intensity domain where bilateral asymmetry has been demonstrated to occur by previous studies (4, 8).

Carpes et al. examined the effects exercise intensity had on bilateral asymmetry in mean crank torque in trained cyclist (111). At intensities < 90% of VO_2max there was a significant difference in peak crank torque between the lower limbs, but above >90% VO_2max asymmetry decreased to the point of non-statistically significant.. However, due to the small sample size of the study (n = 6) the authors suggested using an asymmetry index (AI) to detect differences. The AI suggests that any differences between limbs greater than 10% are considered asymmetrical. Using this technique the results showed that the largest AI between the limbs (25%) was actually at intensities >90 of VO_2max, while intensities <90% VO2max induced the lowest AI (<10%). Additionally Carpes et al. examined mean crank torque asymmetry at intensities between 60 and 70% of VO_2max and found AI that ranged from 2 to 16% (82). The authors noted that when peak crank torque appeared in a lesser magnitude the highest

AIs were present. It was highlighted that AI changed systematically with crank torque and exercise intensity, and it was suggested that this was due to fatiguing of the dominant limb.

Due to the heterogeneous nature of MS standard statistical analysis may not detect the presence of various symptoms, such as bilateral asymmetry, when examining them based on group averages. Therefore it may be appropriate to use techniques, such as the AI index put forth by Carpes et al., to assess asymmetry in addition to standard statistical analysis. During the self-selected cadence condition in the MS group, the AI for 50, 60, and 70% were 16.7 ± 17.1%, 13.9 ± 15.3%, and 12.4 ± 12.1% respectively; indicating the presence of asymmetry in this group. However, in the Non-MS group the AI for the same relative intensities during the self-selected cadence condition did not reach levels that would indicate the presence of asymmetry, 6.26 ± 5.37%, 5.21 ± 4.08%, and 3.63 ± 3.93% respectively. Similar values from the self-selected cadence were seen for both groups during the high cadence condition, indicating the presence of asymmetry at 50, 60, and 70% in the MS group while no asymmetry was present for the Non-MS group. During the low condition an AI of >10% was only present during the 50% intensity stage for the MS group, while no stages had an AI of >10% in the Non-MS group. When examining the average asymmetry seen throughout each of the three cadence conditions for both groups the MS group had an AI of > 10% for the self-selected, high, and low conditions (31.69 ± 51.3%, 23.4 ± 38.9%, and 23.4 ± 38.9% respectively) while the Non-MS group's AI remained at <5% during all three conditions. The levels of AI seen in the current study are similar to those seen by previous studies mentioned earlier (4, 8).

Previously it has been reported that cadence has a significant impact on levels of asymmetry during cycling in trained and non-trained healthy controls. Currently there is no conclusive relationship between pedaling rate and asymmetry levels (18, 21, 83). No real discernable pattern existed in the current data set as well. We had speculated that by increasing the number of muscular contractions an individual was performing at the same relative and absolute power output this would require an increase in the propagation of action potentials from the central nervous system (CNS) to the peripheral musculature. In theory this increase would increase the strain on the CNS leading to earlier task failure via neuromuscular fatigue. We had planned on assessing this greater rate of development of neuromuscular fatigue via EMG and the RMS amplitude. However, we were not able to collect a sufficient sample for analysis. We can however comment on the TTE and % of PPO that participants reached during each trial. No large differences were of note between all the conditions in the Non-MS group, and very little differences existed between the Self-Selected and Low cadence conditions for TTE (13 secs) and %PPO (2.2%) in the MS group. When comparing these two conditions to the High cadence large differences begin to appear. TTE occurred 165 and 152 secs sooner compared to the Self-Selected and Low cadences. Participants reached task failure at a power output 10% and 12.2% lower compared to the Self-Selected and Low cadence. We can speculate that the High cadence condition induced a greater rate of fatigue development in the MS group than the Self-Selected and Low cadences. The nature of the fatigue (neuromuscular vs. metabolic) cannot be fully determine with the current data set.

EDSS is an incremental scale used to assess the level of physical disability associated with multiple sclerosis (29). Higher EDSS scores are often associated with greater disease progression. In order to determine the relationship between EDSS scores and the level of asymmetry for contribution to total power output in the lower limbs Pearson's r correlations were ran. A positive significant relationship was found between EDSS scores and asymmetry across all, indicating that the higher the disability status the higher the levels of asymmetry. This could help explain the lack of significant findings in the current study. The average EDSS score in the MS group of the current study was 2.0 ± 2.04, indicative of minimal disability. It can be speculated that asymmetry may not be detectable or reach significant levels until higher EDSS scores are reached.

Maximal Voluntary Contractions

Bilateral asymmetry in isometric knee extensor strength has been observed in persons with MS in previous literature with mixed results. Chung et al. 2005 and 2008 on both occasions observed no statistically significant differences for peak isometric torque and isometric strength asymmetry in the knee extensors (6, 7). Larson et al. observed a statistically significant difference in maximal voluntary isometric contraction (MVIC) strength of the knee extensors between limbs in the MS group with no statistically significant difference between the limbs in the Non-MS group (4). The difference between the limbs was also statistically significantly greater in the MS group compared to the Non-MS group. The results of the current study are in agreement with the findings of Chung et al., and in contrast with those of Larson et al. (4, 6, 7). However, the current study reported a similar isometric strength asymmetry score in the

MS group, 20.6 ± 19.8 %, compared to Larson et al., 18.2 ± 9.4 %. The values in the Non-MS group, 18.0 ± 4.1 %, of the current study are greater than that reported by Larson et al., 11.3 ± 7.9 %. The large amount of asymmetry present in the Non-MS group, compared to previous literature, could possibly explain the lack of significant findings despite similar asymmetry scores in the MS-group compared to previous studies. Differences in statistical analysis could also provide some explanation as well. Larson et al. performed analysis on the absolute difference between the limbs after classifying the limbs as strong and weak. Whereas the current study utilized asymmetry scores which provide a better indication of the magnitude of difference rather than just absolute difference. This difference in findings is interesting as the MVC methodology used in the current study mimicked that of Larson et al. (4).

As mentioned previously the amount of asymmetry seen in the Non-MS group of the current study was larger compared to the Non-MS groups of previous literature (4). Limited research has been performed examining strength asymmetry of the lower limbs in younger healthy adults that are not trained athletes. Perry et al. 2006 examined the relationship between age and lower limb strength asymmetry in the knee and ankle extensors. Significantly greater levels of asymmetry in knee extensor asymmetry was observed in the older group (76.4 ± 0.8 yrs) compared to the younger group (29.3 ± 0.6 years). However, the amount of asymmetry observed by Perry et al. (8 to 14%) was still less than that observed in the current study. Due to the lack of research in this area further investigation would be beneficial for identifying the amount of lower limb strength asymmetry in a young healthy non-athletic cohort.

Functional Performance Tests

Both the 25WT and 6MWT are common functional performance tests administered when evaluating persons with MS (13, 39, 77). The 25WT is a part of the Multiple Sclerosis Functional Composite Score, and has been shown to be a good measure of overall walking ability in clinical populations (91). The 6MWT has been shown to be a good indicator of muscle and walking endurance in persons with MS, and is considered to be a good indicator of the exercise level of activities of daily living Lower performance on functional performance tests such as the 25WT and 6MWT in persons with MS compared to those without has been observed in previous literature (91, 112, 113). However, the results of the current study are in contrast with the results of previous studies. The current study found no statistically significant difference in performance on both the 25WT and 6MWT between the MS group and Non-MS group. Again, the potential differences found in the current study compared to the previous literature could be related to the average level of disability in the cohort in the current study. The average EDSS in the current study was reported to be 2.0 ± 2.4, this indicates a minimal level of disability. This suggests that the current cohort's disease progression may not have a severe impact on physical function.

Relationship between Walking Performance and Physiological Variables

Pearson's correlation coefficients were examined to assess the relationship between isometric strength asymmetry, VO_2max, PPO, Asym. Self-Selected, and performance on the 25WT and 6MWT. We examined these relationships first by pooling all subjects together to increase the sample size and reduce type II error. In the Pearson's correlations of the pooled subjects VO_2max (r = -0.61), PPO (r = -0.64), and

Asym. Self-Selected (r = 0.91) were significantly correlated with performance on 25WT. Additionally, VO_2max (r = 0.76), PPO (r = 0.79), and Asym. Self-Selected (r =-0.76) were significantly correlated with performance on 6MWT. These relationships indicate that individuals with a higher VO2max and PPO require less time to walk 25 feet and can walk a greater distance in 6 minutes. The relationship between Asym. Self-Selected indicate that those persons with larger amounts of asymmetry require more time to cover 25 feet and cover less distance during 6 minutes of walking. To our knowledge this is one of the first studies to examine the relationship between levels of asymmetry during double leg cycling and functional performance measures, indicating that higher levels of asymmetry have a negative impact on walking performance.

To investigate if the MS group exhibited correlations between the physiological variables and the functional performance tests, Pearson's correlations were examined in each group independently. The results indicated that significant correlations in the MS group existed between VO2max (r = -0.75), PPO (-0.82), Asym. Self-Selected (r = 0.91), and performance during the 25WT. In contrast the Non-MS group did not exhibit any significant correlations between the physiological variables and 25WT performance. The correlations seen in the MS group reflect a similar finding in the pooled data, such that individuals with a higher VO2max and PPO required less time to walk 25 feet and those with larger amounts of asymmetry require more time to walk 25 feet.

The MS group also exhibited significant correlations between VO_2max (r = 0.87), PPO (0.87), Asym. Self-Selected (r = -0.82), and distance covered during the 6MWT. The Non-MS group did show a significant correlation between PPO (r = 0.76)

and distance covered during the 6MWT. These relationships in the MS group are again similar to those seen in the pooled subjects, such that persons with higher a VO_2max and PPO are able to walk a greater distance over 6 minutes and those with larger amounts of asymmetry.

An interesting finding from the current study was the absence of a significant relationship between knee extensor strength asymmetry and performance on the 25WT and 6MWT. Previously strength asymmetry in knee extensors as well as the knee flexors has been shown to be strongly correlated to walking ability in MS patients (7, 114, 115). The previous literature reported statistically significant differences between isometric strength asymmetry of the knee extensors between person with MS and without. However, the current study did not observe this difference, and potentially could explain the differences seen in the relationship between walking performance and isometric strength asymmetry. As reported earlier the average EDSS scores for the current study indicated a minimal level of disability suggesting little to no impact on walking capabilities.

Electromyography during Cycling

Although we were not able to perform our intended analysis for the EMG data, alternative analysis was conducted. We examined the average RMS amplitude for each exercise intensity and expressed it as a percentage of the maximal RMS amplitude. No significant differences were observed between the limbs and conditions. However, due to the small viable sample size an increased risk for type II error is present. We observed very high RMS amplitudes (60 to 75%) at the lowest exercise intensity (50% of PPO). The highest observed RMS amplitude observed during the 50% exercise

intensity stage was in the high cadence condition. Starting at such a high percentage of maximal RMS amplitude may potentially provide some explanation for the quicker termination of exercise during this condition. We can speculate that the higher number of muscular contractions may have put a larger strain on the CNS, especially when comparing at the 50% stage, potentially leading to a greater rate of development of neuromuscular fatigue. However, when examining the slope coefficients between exercise intensities within each condition no significant differences were present. Again, due to the small viable sample size for this analysis the risk of type II error is increased.

Determination of the Presence of Bilateral Asymmetry in MS

Bilateral asymmetry is still an emerging topic in MS research. Although bilateral asymmetry in cycling performance and MVC strength has been observed in previous literature, the current study did not find a statistically significant difference in asymmetry levels for cycling performance and MVC strength between an MS group and Non-MS group (4, 5, 8). Upon further examination, similar effect sizes for asymmetry levels in cycling performance and MVC strength were observed in the current study compared to previous literature (4). When using alternative analysis methods, such as the 10% AI, for the average asymmetry during each cadence condition significant levels of asymmetry were present in the MS group for both the Self-Selected and High cadence conditions while the Non-MS group did not show significant asymmetry levels for any cadence conditions. In fact, 6 participants from the MS group had an average asymmetry greater than 10% during the Self-Selected cadence condition. Seven had significant levels of asymmetry during the High cadence condition, and 4 for the Low

cadence condition. The MS group displayed asymmetry levels two to three times that of the Non-MS group across all cadence conditions. We believe that the current study highlights the limitations of using traditional statistical analysis when researching a disease with a very heterogeneous nature, such as MS. We believe that in order to properly assess the presence of some symptoms, such as bilateral asymmetry, additional analysis such as effect sizes or thresholds should be used for the use of determining meaningful and clinical significance to allow for analysis on an individual and group basis. This not a ground breaking notion as the AI index of 10% has been used in previous literature for assessing asymmetry during cycling in trained and untrained individuals (17, 20, 22, 111). A recent study with MS chose to focus on effect size estimates, rather than statistical significance, as an approach for identifying meaningful differences between groups (116). The same group adopted a benchmark of 0.5 standard deviation as an indication of meaningful difference between groups (116, 117). We believe that these additional methods for the determination of significance have an appropriate application for an MS cohort.

CHAPTER V: CONCLUSIONS

The bilateral asymmetry in the contribution of each limb to the total power output during double leg cycling was assessed at 50, 60, and 70% of PPO and across three distinct cadence conditions (Self-Selected, High, and Low) in a sample of MS and Non-MS participants to determine if a significant difference between the two groups, the three intensities, and three cadence conditions existed. Significant differences in asymmetry were not observed between groups, intensities, and conditions. However, using the suggested 10% AI methodology for determining asymmetry during cycling, asymmetry was present in the MS group at the 50, 60, and 70% intensities for both the Self-Selected and High condition and the 50% intensity in Low condition. An AI of >10% was not observed at any intensities or conditions in the Non-MS group. MVCs were conducted to assess strength asymmetry in the knee extensors, and no significant differences existed between the MS group and Non-MS group. The current study is one of the first to explore the relationship between bilateral asymmetry during double leg cycling and walking performance. It was observed that bilateral asymmetry during double leg cycling has a negative impact on walking performance.

Answer to Research Questions

First Research Question

Do persons with MS exhibit greater bilateral asymmetry in power production contribution during a double leg graded exercise test compared to healthy controls? It was hypothesized that individuals with MS would exhibit greater bilateral differences in power output during a double leg cycling graded exercise test compared to healthy controls. We did not observe a significant difference

between the MS group and Non-MS group in asymmetry in contribution to total power production between the lower limbs. Our hypothesis was not supported by our data and was rejected.

Second Research Question

Is there a bilateral difference in muscle activation during double leg cycling in persons with MS? It was hypothesized that a bilateral difference in muscle activation during double leg cycling in persons with MS would exist. Due to complications during data collection an sufficient sample size to adequately address this question was not obtained. Thus this question cannot be fully addressed currently.

Third Research Question

Does exercise intensity and cadence selection affect the physical manifestation of bilateral asymmetry in persons with MS? We hypothesized that the manipulation of exercise intensity and cadence would have a significant effect on the physical manifestation of bilateral asymmetry. We did not observe a significant difference between the MS group and Non-MS group in asymmetry between conditions and intensities. Our hypothesis was not supported by our data and was rejected.

Fourth Research Question

Do persons with MS exhibit greater bilateral asymmetry in isometric strength of the knee extensors compared to healthy controls? We hypothesized that persons with MS would exhibit greater bilateral asymmetry in isometric strength of the knee extensors compared to healthy controls? We did not observe significant differences between the MS group and Non-MS group in isometric strength

asymmetry in the knee extensors. Our hypothesis was not supported by our data and was rejected.

Clinical Significance

Bilateral asymmetry has been reported previously in persons with MS, and these asymmetries have a significant impact in their daily life. Often impairments in functional capacity prevents individuals with MS from being able to perform activities of daily living and participating in regular exercise leading to an elevated risk of the development of comorbidities. One area that remained unclear was the impact of exercise intensity on the physical manifestation of bilateral asymmetry in persons with MS. More specifically, whether or not exercising at submaximal intensities induced large amounts of bilateral asymmetry in the lower limbs. The results of this study suggest that exercise intensity does not impact the manifestation of bilateral asymmetry as similar levels of asymmetry were seen between submaximal intensities in the MS group, and were not statistically significantly different from the Non-MS group. This could potentially provide justification for the prescription of exercise at various submaximal intensities in persons with MS, as it will not increase asymmetry and potentially increase risk for falls. An important finding of the current study was the strong negative relationship between bilateral asymmetry in contribution to total power production during double leg cycling and performance in both the 25WT and 6MWT. If a person with MS is exhibiting decrements in walking performance, a potential solution could be to prescribe an exercise training protocol with the aim to reduce bilateral asymmetry in the lower limbs. Although the current study did not observe any statistically significant differences when examining group means and variance, when

using an asymmetry index it was determined that large amounts of asymmetry were present in the MS group compared to the Non-MS group. This observation highlights a common issue that occurs when researching diseases that are heterogeneous in nature. Often the presence of an effect or symptom can be masked when examining group means, but when alternative methods are used that allow for observations to be performed on a group and individual level it can be detected. A need for a better form of analysis to detect effects or symptoms is needed for researching persons with MS. The evaluation of asymmetry highlights a facet of physiological performance that cannot be detected when simply assessing walking capacity or VO_2max. The assessment of asymmetry identifies muscular imbalances that potentially identifies individuals with fall risk, but also provides insight for proper exercise prescription. By evaluating asymmetry, practitioners can prescribe specific exercise modalities with the aim of reducing asymmetry.

Future Directions

Both the results and unforeseen issues during data collection with the current study provide insight and direction for future research. We speculate that reasons for differences in the findings of bilateral asymmetry during cycling in the current study compared to the previous literature may pertain to methodological differences. Previous studies have assessed bilateral asymmetry in power production only at PPO and during single leg cycling. The current study aimed to assess bilateral asymmetry from 50% to 100% of PPO, but the cumulative fatigue of the protocol potentially induced the earlier task failure in the current study that prohibited being able to examine asymmetry at higher intensities. Future studies may benefit from using a discontinuous protocol that

allow for several minutes of rest after 3 minute trails at various exercise intensities to inhibit the development of peripheral fatigue due to the accumulation of metabolites such as lactate and H^+. This will allow for the examination of bilateral asymmetry across all exercise intensities and domains. The current MS sample possessed a low EDSS score that corresponds to minimal levels of disability. This more than likely impacted the results of the current study. Future research with bilateral asymmetry would benefit from recruiting individuals that have higher levels of disability.

Limitations

As with any study the limitations associated with the current study need to be addressed. First of all, due to a rather small sample size some of the comparisons made were underpowered and additional significant differences may have been observed if more participants had been enrolled. This does not mean those results are any less meaningful as many had large effect sizes. Also, the results are only representative of those who completed the study, who were 23 to 61 years of age and had a diagnosis of relapse-remitting MS. Another limitation to the current study was the ability to only observe bilateral asymmetry at submaximal intensities and not being able to assess at higher intensities like previous studies. Fatigue is always a limitation when studying persons with MS. However, fatigue was controlled to the best of our ability using tow common fatigue questionnaires. The current study assessed bilateral asymmetry during cycling rather than during walking due to availability of equipment and safety concerns. Both cycling and walking are bipedal movements that involve the limbs working in a dependent manner. Cycling allowed for the assessment of bilateral asymmetry at precise

relative exercise intensities without the fear of falling. Ideally, asymmetry would have been assessed during walking, but cycling served as an appropriate replacement.

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Appendix A: IRB Approval, Consent Form, and Hippa

The UNIVERSITY of OKLAHOMA

Institutional Review Board for the Protection of Human Subjects

Initial Submission – Board Approval

Date: June 23, 2017

IRB#: 8069
Meeting Date: 05/22/2017
To: Rebecca D Larson, PhD
Approval Date: 06/22/2017
Expiration Date: 04/30/2018

Study Title: Differences in Muscle Activation and Force Contribution during Cycling in Individuals with Multiple Sclerosis

Reference Number: 665702

Study Status: Active - Open

At its regularly scheduled meeting the IRB reviewed the above-referenced research study. Study documents associated with this submission are listed on page 2 of this letter. To review and/or access the submission forms as well as the study documents approved for this submission, open this study from the *My Studies* option, click to open this study, look under Protocol Items to click on the current *Application*, *Informed Consent* and *Other Study Documents*.

If this study required routing through the Office of Research Administration (ORA), you may *not begin your study yet*, as per OUHSC Institutional policy, until the contract through ORA is finalized and signed.

As principal investigator of this research study, it is your responsibility to:

- Conduct the research study in a manner consistent with the requirements of the IRB and federal regulations at 45 CFR 46 and/or 21 CFR 50 and 56.
- Request approval from the IRB prior to implementing any/all modifications.
- Promptly report to the IRB any harm experienced by a participant that is both unanticipated and related per IRB Policy.
- Maintain accurate and complete study records for evaluation by the HRPP quality improvement program and if applicable, inspection by regulatory agencies and/or the study sponsor.
- Promptly submit continuing review documents to the IRB upon notification approximately 60 days prior to the expiration date indicated above.

In addition, it is your responsibility to obtain informed consent and research privacy authorization using the currently approved, stamped forms and retain all original, signed forms, if applicable.

If you have questions about this notification or using iRIS, contact the IRB at 405-271-2045 or irb@ouhsc.edu.

Sincerely,

Martina Jelley, MD, MSPH
Chairperson, Institutional Review Board

1105 N. Stonewall Avenue, Oklahoma City, OK 73117 (FWA0007961)

Consent Form
University of Oklahoma Health Sciences Center (OUHSC)
University of Oklahoma-Norman

Differences in Muscle Activation and Force Contribution during Cycling in Individuals with Multiple Sclerosis

Principal Investigator: Rebecca D. Larson, PhD

This is a research study. Research studies involve only individuals who choose to participate. Please take your time to make your decision. Discuss this with your family and friends.

Why Have I Been Asked To Participate In This Study?
You are being asked to take part in this study because you have been diagnosed with Multiple Sclerosis (MS) or you are a healthy control.

Why Is This Study Being Done?
The purpose of this study is to determine how much of a difference exists in the force produced by the right leg and left leg during cycling. Secondly, to determine if the size of the difference in force production between the legs affects an individual's ability to perform tests that measure functional capacity.

How Many People Will Take Part In The Study?
About 60 people (30 individuals with MS and 30 healthy individuals) will take part in this study. All testing visits will occur in the Body Composition and Human Performance Lab at the University of Oklahoma.

What Is Involved In The Study?
If you agree to participate, we will ask you to participate in a 6 visit study where we will assess your fitness level and bilateral asymmetry on 5 occasions. The first visit of the study (Visit 1) will be used to familiarize subjects with: the 6-minute walk test (6MW), 25-Foot Walk (25FW), maximal voluntary isometric contractions (MVICs), graded exercise test (GXT). Following familiarization, a full body dual energy x-ray absorptiometry (DXA) scan will be performed to assess fat and fat-free mass. Following this, one scan for each side of your hip will be done for a total of three scans. Visit 2 through 5 will consist of performing a graded exercise test at a set pace (revolutions per minute)(rpm) while wearing electromyography (EMG) electrodes to assess muscle activation. On Visit 6 (final) subjects will perform the functional tests familiarized with on Visit 1, as well as MVICs while wearing EMG electrodes.

Prior to the first visit of the study both research and control participants must obtain a signed medical clearance letter and given to the research team. The neurologist and physician are not a part of the research team and will be selected by the study participants.

Visit #1

During the first visit we will discuss the purpose of the study, and then explain the details of each visit. If you decide to participate you will be asked to read and sign this informed consent. You will also fill out questionnaires regarding your physical health and quality of life.

Forms and Questionnaires (Visit 1 Only): Written and verbal descriptions of the experiment will be provided, and any questions will be answered. You will be asked to fill out a physical activity readiness questionnaire (PAR-Q), medical history/health screening questionnaire, a modified fatigue impact scale questionnaire, and a Rochester fatigue diary.

Familiarization: the purpose of the familiarization with testing procedures is for you to become accustomed to the procedures of the experiment.

The 6MW consist of walking a course of 30 meters in length for 6 minutes. The goal of the test is to walk as far and as long as possible without running or jogging. You are free to speed up and slow down accordingly.

25FW will consist of you walking in a straight line when instructed for 25 feet as quickly and as safely as possible

After the functional tests, you will then be fitted and familiarized to a specialized machine called an isokinetic dynamometer (Kin Com) which will be used to measure the strength of your lower legs. You will be seated on the Kin Com and adjustments will be made to ensure comfort and proper fit using safety straps around the waist, chest, and testing leg. You will be asked to perform submaximal efforts (contractions) until you feel comfortable with the device. Submaximal contractions require you to perform he exercise at low intensities that are less than maximal effort. You will perform an isometric contraction which is similar to pushing against a stationary object (ex. Pushing against a wall). You will be fitted and familiarized for both legs and for all three muscle groups being tested: knee extensors, knee flexors, and plantar flexors. The adjustments made to the seat of the dynamometer, to ensure comfort and proper fit,will be recorded to be used in subsequent testing visits.

Next, you will be asked to ride a cycle ergometer (a computer interfaced bike), at low intensities, while wearing a mouthpiece, nosepiece and headgear that enable us to observe information about your breathing. The cycle ergometer is equipped with independent power meters that allow us to observe the force that each leg is placing on the pedals while cycling. You will pedal at a light effort to allow you to become familiar with the equipment and breathing into the mouthpiece. Handle bar and seat positions will be recorded for use in future studies.

Finally, you will be asked to undergo a dual X-ray absorptiometry (DXA) scan in order to determine fat mass and lean mass of your legs. This is a non-invasive procedure that

requires you to lie down as still and as quietly as possible for approximately 10 minutes. If you participate in this research you will be exposed to radiation from the DXA scans. These scans are for research purposes only, and are not necessary for your medical care. The radiation exposure is equivalent to less than the daily amount of natural background radiation exposure people in the United States receive. The risk from radiation exposure of this magnitude is too small to be measured directly. This study may be hazardous to an unborn child. You will be asked to perform a simple urine test to determine possible pregnancy. The test will be free. A negative pregnancy test is needed prior to having a DXA scan performed. For unexpected pregnancies, subjects are encouraged to speak with their family physician.

Visit 1 will take approximately 120 minutes

Visit 2

You will then be asked to urinate (in a private bathroom) and collect a small urine sample so we can check your hydration status based on the specific gravity of your urine (how dilute or concentrated). If your hydration status indicates that you are dehydrated you will be asked to consume fluids and return for your test later in the day. Next, we will perform basic measurements (height and weight) and resting measurements for heart rate, blood pressure, and blood lactate. Prior to exercise testing electromography (EMG) electrodes will be placed on the muscle belly of the vastus lateralis and vastus medialis (muscles in your legs) to assess muscle activation during cycling. Prior to application of electrodes your skin must be prepped by shaving any hair in the region of electrode application, a gentle abrasion to remove any debris, and cleansing with rubbing alcohol. Once completed, electrodes will be placed on your skin. Next, you will be asked to ride a cycle ergometer (a computer interfaced bike), at set intensities, while wearing a mouthpiece, nosepiece and headgear that enable us to observe information about your breathing. You will be allowed to determine the pace (rpm) you would like to cycle at. The protocol will begin with 1 minute of rest, followed by a 5 minute warmup at a low intensity. After the warmup, testing will begin. Every three minutes the cycle ergometer will be adjusted so that it is harder for you to pedal. At the end of each 3 minute stage you will be asked how hard you are working using a 0-20 scale (0 being very easy and 20 being the hardest effort) and heart rate and lactate will be assessed. Heart rate will be measured using a chest strap sensor and lactate will be taken with a finger prick to collect a small drop of blood. You will be asked to pedal the cycle until you can no longer maintain your preferred pace within 10 rpm.

Visit 2 will last approximately 60 minutes

Visit #3

You will return to the laboratory at least 48 hours after visit 1 but no more than 168 hours (1 week) to complete your third visit. You will then be asked to urinate (in a private bathroom) and collect a small urine sample so we can check your hydration status based on the specific gravity of your urine (how dilute or concentrated). If your hydration status

indicates that you are dehydrated you will be asked to consume fluids and return for your test later in the day. You will again be asked to perform a graded exercise again. This will a different protocol from the one used on Visit 2. We will use the data collected from Visit 2 to customize the protocol so that the stages of the test are equivalent to 60, 70, 80, 90, and 100% effort. The same procedure will be followed for the application of EMG electrodes to the muscle belly of the vastus lateralis and vastus medialis. The pace or rpm you will be asked to pedal at today will be randomly selected from: 60-70 (low), preferred, and 90-100 (high). You will be given one minute of rest at the beginning of the graded exercise test, followed by 5 minutes warmup at a light intensity. After the warmup testing will begin. Every three minutes the cycle ergometer will be adjusted so that it is harder for you to pedal. At the end of each 3 minute stage you will be asked how hard you are working using a 0-20 scale (0 being very easy and 20 being the hardest effort) and heart rate and lactate will be assessed. Heart rate will be measured using a chest strap sensor and lactate will be taken with a finger prick to collect a small drop of blood. You will be asked to stay as close as possible to the selected pace range. If you drop out of the desired pace range the test will be concluded.

Visit 3 will last approximately 60 minutes

Visit #4

You will return to the laboratory at least 48 hours after Visit 3 but no more than 168 hours (1 week). The same procedures will be followed as in Visit 3, but the pace will be selected from the two remaining options not performed on Visit 3.

Visit 4 will last approximately 60 minutes

Visit #5

You will return to the laboratory at least 48 hours after Visit 4 but no more than 168 hours (1 week). The same procedures will be followed as in Visit 3 and 4, but the pace will be selected from the one remaining options not performed on Visit 3 or Visit 4.

Visit 5 will last approximately 60 minutes

Visit #6

On this visit you will be asked to perform the 2 functional tests (6 minute walk and 25 foot walk) and the maximal voluntary isometric contractions you have been familiarized with on Visit 1. The only difference will be that you will wear the EMG electrodes on your vastus lateralus and vastus medialis during the MVICs.

The 6MW consist of walking a course of 30 meters in length for 6 minutes. The goal of the test is to walk as far and as long as possible without running or jogging. You are free to speed up and slow down accordingly.

25FW will consist of you walking in a straight line when instructed for 25 feet as quickly and as safely as possible

After the functional tests, you will be prepped for the placement of EMG electrodes (following the same procedure on Visit 2-5). Once EMG electrodes have been applied, you will then be setup on a specialized machine called an isokinetic dynamometer (Kin Com) which will be used to measure the strength of your lower legs. You will be seated on the Kin Com and adjustments will be made to ensure comfort and proper fit using safety straps around the waist, chest, and testing leg. You will be asked to perform submaximal efforts (contractions) until you feel comfortable with the device. Submaximal contractions require you to perform the exercise at low intensities that are less than maximal effort. You will perform an isometric contraction which is similar to pushing against a stationary object (ex. Pushing against a wall). You will be tested on both legs and for all three muscle groups being tested: knee extensors, knee flexors, and plantar flexors. The leg that is tested first will be randomly selected.

Visit 6 will last approximately 90 minutes.

How Long Will I Be In The Study?
We think that you will be in the study for 2-3 weeks during which you will visit the Body Composition and Human Performance Lab on 6 occasions. Visits will last between 60 and 120 minutes. We think that the total time you will spend performing testing in the lab will be ~450 minutes.

There may be anticipated circumstances under which your participation may be terminated by the investigator without regard to your consent.

- If it is determined to be in your best medical interest.
- Your condition worsens.
- New information becomes available.
- You fail to follow study requirements.
- If you are pregnant.

You can stop participating in this study at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

What Are The Risks of The Study?
Risks and side effects related to this study include:

Radiation Risk from DXA

If you participate in this research, you will be exposed to radiation from a DXA scan (a type of x-ray). The amount of radiation to which you will be exposed from one DXA scan is approximately less than 1% of the amount of radiation that we are exposed to each

year from natural background sources of radiation. The risk of radiation exposure is cumulative over your lifetime. The DXA scans will be performed for research purposes only and are not required for your medical care.

This study may be hazardous to an unborn child. If you are a pre-menopausal female participant, you will be asked to perform a simple urine test to determine possible pregnancy. There is no cost to you for this test. A negative pregnancy test is needed prior to participating in this study. For unexpected pregnancies, subjects are encouraged to speak with their family physician.

Graded Exercise Test

These tests require that you to exert a maximal effort. The risk for performing these tests is muscle discomfort. You may experience faintness, nausea and/or lightheadedness. You will be closely monitored for any possible ill effects. There is the chance of cardiovascular events from maximal exertion, example of these include increased blood pressure, stroke, myocardial infarction (heart attack), and cardiovascular collapse (sudden death). You will be closely monitored for any possible ill effects. To further decrease your risk of cardiovascular events you will be screened for risk factors.

Maximal Contraction on the Kin-Com Dynamometer

While participating in the study you will be asked to maximally contract you quadriceps, hamstring, and calf muscles which can result in mild discomfort and/or muscle tenderness following contraction. You may find the dynamometer seat or attachments uncomfortable. You may also experience heavier than normal breathing while contracting maximally. While rare and uncommon, you may experience faintness, nausea, and/or lightheadedness. You will be closely monitored for any possible ill effects. To further increase your safety you will screened for risk factors.

Are There Benefits to Taking Part in The Study?

Subjects in both groups will receive personalized information that pertains to their exercise performance and body composition that the subjects can use for their own training.

What Other Options Are There?

You may choose not to participate in the study.

What About Confidentiality? Efforts will be made to keep your personal information confidential. You will not be identifiable by name or description in any reports or publications about this study. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. You will be asked to sign a separate authorization form for use or sharing of your protected health information.

There are organizations outside the OUHSC that may inspect and/or copy your research records for quality assurance and data analysis. These organizations include the US Food & Drug Administration and other regulatory agencies. The OUHSC Human Research Participant Program office, the OUHSC Institutional Review Board, and the OUHSC

Office of Compliance may also inspect and/or copy your research records for these purposes.

What Are the Costs?
There will be no cost to you for participating in this study.

Will I Be Paid For Participating in This Study?
There is no compensation for participating in this study.

What if I am Injured or Become Ill While Participating in this Study?
In case of injury or illness resulting from this study, emergency medical treatment is available. However, you or your insurance company will be expected to pay the usual charge for this treatment. No funds have been set aside by the University of Oklahoma Health Sciences Center, the University of Oklahoma, or to compensate you in the event of injury.

What Are My Rights As a Participant?
Taking part in this study is voluntary. You may choose not to participate. Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. If you agree to participate and then decide against it, you can withdraw for any reason and leave the study at any time. You may discontinue your participation at any time without penalty or loss of benefits, to which you are otherwise entitled.

We will provide you with any significant new findings developed during the course of the research that may affect your health, welfare or willingness to continue your participation in this study.
You have the right to access the medical information that has been collected about you as a part of this research study. However, you may not have access to this medical information until the entire research study has completely finished and you consent to this temporary restriction.

Whom Do I Call If I have Questions or Problems?
If you have questions, concerns, or complaints about the study or have a research-related injury, contact Dr. Rebecca Larson at 352-359-8432 (cell) or 405-325-6325 (office).

If you cannot reach the Investigator or wish to speak to someone other than the investigator, contact the OUHSC Director, Office of Human Research Participant Protection at 405-271-2045.

For questions about your rights as a research participant, contact the OUHSC Director, Office of Human Research Participant Protection at 405-271-2045.

Signature:

By signing this form, you are agreeing to participate in this research study under the conditions described. You have not given up any of your legal rights or released any individual or entity from liability for negligence. You have been given an opportunity to ask questions. You will be given a copy of this consent document.

I agree to participate in this study:

PARTICIPANT SIGNATURE (age ≥18) (*Or Legally Authorized Representative)*	Printed Name	Date
SIGNATURE OF PERSON OBTAINING CONSENT	Printed Name	Date

AUTHORIZATION TO USE or SHARE
HEALTH INFORMATION[1] THAT IDENTIFIES YOU FOR RESEARCH

An Informed Consent Document for Research Participation may also be required.
Form 2 must be used for research involving psychotherapy notes.

Title of Research Project: **Differences in Muscle Activation and Force Contribution during Cycling in Individuals with Multiple Sclerosis**

Leader of Research Team: **Rebecca D Larson, PhD**

Address: **Department of Health and Exercise Science, 1401 Asp Avenue., Room 117 HHC, Norman, OK 73019**

Phone Number: **405-325-6325**

If you decide to sign this document, University of Oklahoma Health Sciences Center (OUHSC) researchers may use or share information that identifies you (protected health information) for their research. Protected health information will be called PHI in this document.

PHI To Be Used or Shared. Federal law requires that researchers get your permission (authorization) to use or share your PHI. If you give permission, the researchers may use or share with the people identified in this Authorization any PHI related to this research from your medical records and from any test results. Information used or shared may include all information relating to any tests, procedures, surveys, or interviews as outlined in the consent form; medical records and charts; name, address, telephone number, date of birth, race, government-issued identification numbers, and can include physical findings from questionnaires, dual X-ray absorptiometry (DXA) scan, graded exercise test (GXT), isometric dynamometer, and functional tests.

Purposes for Using or Sharing PHI. If you give permission, the researchers may use your PHI to determine whether individuals with MS exhibit limb differences in force contribution and muscle activation during a cycling GXT.

Other Use and Sharing of PHI. If you give permission, the researchers may also use your PHI to develop new procedures or commercial products. They may share your PHI with other researchers, the research sponsor and its agents, the OUHSC Institutional Review Board, auditors and inspectors who check the research, and government agencies such as the Food and Drug Administration (FDA) and the Department of Health and Human Services (HHS), and when required by law. The researchers may also share your PHI with no one else.

[1] **Protected Health Information includes all identifiable information relating to any aspect of an individual's health whether past, present or future, created or maintained by a Covered Entity.**

Confidentiality. Although the researchers may report their findings in scientific journals or meetings, they will not identify you in their reports. The researchers will try to keep your information confidential, but confidentiality is not guaranteed. The law does not require everyone receiving the information covered by this document to keep it confidential, so they could release it to others, and federal law may no longer protect it.

YOU UNDERSTAND THAT YOUR PROTECTED HEALTH INFORMATION MAY INCLUDE INFORMATION REGARDING A COMMUNICABLE OR NONCOMMUNICABLE DISEASE.

Voluntary Choice. The choice to give OUHSC researchers permission to use or share your PHI for their research is voluntary. It is completely up to you. No one can force you to give permission. However, you must give permission for OUHSC researchers to use or share your PHI if you want to participate in the research and, if you cancel your authorization, you can no longer participate in this study.

Refusing to give permission will not affect your ability to get routine treatment or health care unrelated to this study from OUHSC.

Canceling Permission. If you give the OUHSC researchers permission to use or share your PHI, you have a right to cancel your permission whenever you want. However, canceling your permission will not apply to information that the researchers have already used, relied on, or shared or to information necessary to maintain the reliability or integrity of this research.

End of Permission. Unless you cancel it, permission for OUHSC researchers to use or share your PHI for their research will never end

Contacting OUHSC: You may find out if your PHI has been shared, get a copy of your PHI, or cancel your permission at any time by writing to:

Privacy Official University of Oklahoma Health Sciences Center PO Box 26901 Oklahoma City, OK 73190	or	Privacy Board University of Oklahoma Health Sciences Center PO Box 26901 Oklahoma City, OK 73190
If you have questions, call: (405) 271-2511	or	(405) 271-2045.

Access to Information. You have the right to access the medical information that has been collected about you as a part of this research study. However, you may not have access to this medical information until the entire research study is completely finished. You consent to this temporary restriction.

Giving Permission. By signing this form, you give OUHSC and OUHSC's researchers led by the Research Team Leader permission to share your PHI for the research project listed at the top of this form.

Patient/Participant Name (Print): _____

_____ _____
Signature of Patient-Participant Date
or Parent if Participant is a minor

Or

_____ _____
Signature of Legal Representative** Date

**If signed by a Legal Representative of the Patient-Participant, provide a description of the relationship to the Patient-Participant and the authority to act as Legal Representative:

_____
OUHSC may ask you to produce evidence of your relationship.

A signed copy of this form must be given to the Patient-Participant or the Legal Representative at the time this signed form is provided to the researcher or his representative.

Appendix B: Modified Fatigue Impact Scale, Health History Questionnaire, and Kurtzke Questionnaire

Patient's Code: _____ Date: _____/_____/_____
month day year

Test#: 1 2 3 4 5 6

MODIFIED FATIGUE IMPACT SCALE (MFIS)

INSTRUCTIONS

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

Because of my fatigue during the **past 4 weeks…**

	Never	Rarely	Sometimes	Often	Almost Always
1. I have been less alert.	0	1	2	3	4
2. I have had difficulty paying attention for long periods of time.	0	1	2	3	4
3. I have been unable to think clearly.	0	1	2	3	4
4. I have been clumsy and uncoordinated.	0	1	2	3	4
5. I have been forgetful.	0	1	2	3	4
6. I have had to pace myself in my physical activities.	0	1	2	3	4
7. I have been less motivated to do anything That requires physical effort	0	1	2	3	4
8. I have been less motivated to participate in social activities.	0	1	2	3	4
9. I have been less motivated to do things away from home.	0	1	2	3	4

Date:___/___/___
Initials:_____

IRB NUMBER: 8069
IRB APPROVAL DATE: 06/22/2017

	Never	Rarely	Sometimes	Often	Almost Always
10. I have had trouble maintaining physical effort for long periods.	0	1	2	3	4
11. I have had difficulty making decisions.	0	1	2	3	4
12. I have been less motivated to do anything that requires thinking.	0	1	2	3	4
13. my muscles have felt weak.	0	1	2	3	4
14. I have been physically uncomfortable.	0	1	2	3	4
15. I have had trouble finishing tasks that require thinking.	0	1	2	3	4
16. I have had difficulty organizing my thoughts when doing things at home or at work.	0	1	2	3	4
17. I have been less able to complete tasks that require physical effort.	0	1	2	3	4
18. my thinking has been slowed down.	0	1	2	3	4
19. I have had trouble concentrating.	0	1	2	3	4
20. I have limited my physical activities.	0	1	2	3	4
21. I have needed to rest more often or for longer periods.	0	1	2	3	4

Date:___/___/___
Initials:_____

Date: _____

MS-Medical History
Participation Information

Name: _____ Date of Birth: _____

Address: _____ Phone number: (w) _____

_____ (h) _____

Email: _____

Blood Pressure:_____/_____ (cell) _____

Height: _____ Weight: _____

Gender: Male Female (circle)

Ethnicity : Caucasian African American Hispanic Asian Other

Emergency contact name and number: _____

Family Physician name and number: _____

Please answer the following questions:

I. GENERAL HEALTH

1. Have you been diagnosed with diabetes? **Y** **N**
   If "yes", please explain _____
2. Have you ever had an oral glucose tolerance test? **Y** **N**
   If "yes", please explain _____
3. Have you ever been told by a physician that you have Osteoporosis/Osteopenia? **Y** **N**
4. Have you ever been told by a physician that you have a heart condition? **Y** **N**
3. Have you or anyone in your immediate family had a heart attack, stroke, or cardiovascular disease before age 50 yrs? If "yes," please explain. **Y** **N**
   _____
5. Have you ever been told by a physician that you have high blood pressure? **Y** **N**
6. Have you ever been told by a physician that you have high cholesterol? **Y** **N**
7. Have you ever been told by a physician that you have thyroid problems? **Y** **N**

If you answered yes, please define (hypothyroidism or hyperthyroidism) _____

Date: _____

8. Have you ever been told by a physician that you have kidney disease? **Y** **N**

9. Do you feel angina-like symptoms (pain or pressure in your chest, neck, shoulders, or arms) during or after physical activity? **Y** **N**

10. Do you ever lose your balance because of dizziness? **Y** **N**

11. Do you ever lose consciousness? **Y** **N**

12. Do you consider most of your days very stressful? **Y** **N**

13. Do you consider your eating habits healthy overall? **Y** **N**
(Lower in fats and fried foods, higher in fruits, veggies and grains)

14. Have you had any major surgeries, or any surgery that required incisions?
Y **N**
If "yes", please explain: _____

15. Do you consider yourself to be generally healthy? **Y** **N**

16. Do you currently smoke cigarettes or cigars or chew tobacco? **Y** **N**
If "yes", how often and how much: _____

17. Are you a former smoker? **Y** **N**
If so, how long has it been since you quit smoking? _____

18. Has your weight changed more than 5 pounds in the last 6 months? **Y** **N**

EARS:
_____ hearing difficulty
_____ ringing
_____ pain
_____ discharge
_____ other

NOSE:
_____ bleeding
_____ difficulty smelling
_____ nasal congestion
_____ sinus problems
_____ other

Please explain _____

PULMONARY:
_____ shortness of breath
_____ wheezing
_____ asthma
_____ chronic cough
_____ allergies
_____ other

Please explain _____

19. Are there any other health-related issues we should know about? _____

Date: _____

Please explain _____
_____

II. MEDICATION/SUPPLEMENTS

1. Please list all of the **prescription medications** you are currently taking.

Medicine name	Amount taken per day	Months/years on the medication	Reason
a. _____	_____	_____	_____
b. _____	_____	_____	_____
c. _____	_____	_____	_____
d. _____	_____	_____	_____
e. _____	_____	_____	_____
f. _____	_____	_____	_____

2. Any known allergies? Explain _____

3. Have you been on steroid medication in the past? **Y** **N**
   If so, please explain in detail _____
   _____
   _____

4. Please list all of the **over-the-counter medicines or supplements** (including vitamins that you take regularly)

Item name	Amount taken per day	Months/years on medication	Reason
a. _____	_____	_____	_____
b. _____	_____	_____	_____
c. _____	_____	_____	_____
d. _____	_____	_____	_____
e. _____	_____	_____	_____
f. _____	_____	_____	_____

Date: _____

III. REPRODUCTIVE STATUS (If male, skip to section IV)

1. Have you reached menopause? (if NO skip to Section IV) **Y N**

2. How long has it been since you reached menopause? _____ **Y N**

3. Do you still have your ovaries? _____ **Y N**
   a. If not, how old were you when they were removed? _____.

4. Have you ever been on hormone replacement therapy?

   a. If so, are you still taking hormone replacement therapy? **Y N**

   b. If you have previously taken hormone replacement therapy, but have since stopped, when did you stop taking hormone replacement therapy?
   _____

5. Have you ever taken osteoporosis medications? **Y N**

   Which ones and for how long? _____
   _____

IV. OSTEOPOROSIS/FRACTURE/BONE HEALTH SECTION

1. Have you ever had a bone scan? **Y N**
   If so, what year? _____
   What was the outcome?_____

2. Please provide a list of any bone fractures you have had in the past.

Bone	Cause (fall, accident, etc)	Year
_____	_____	
_____	_____	

3. Did a doctor tell you that any of these fractures were due to osteoporosis/osteopenia? **Y N**

4. Is your diet low in dairy products (≤ 3 servings/day)?
   Y N

5. Do you take calcium supplements? **Y N**
   If so, how much per day? _____

6. In a typical week, how many alcoholic drinks do you consume? _____

7. Do you drink coffee, tea, or cola products routinely? **Y N**
   About how much coffee, tea, or cola do you drink on an average day? _____-
   _____

Date: _____

8. Do you have a heart valve or implant device such as knee, hip etc.? **Y** **N**

FEAR OF FALLING (Falls Efficacy Scale)

On a scale from 1 to 10, with *1 being very confident and 10 being not confident at all*, how confident are you that you do the following activities without falling?

Activity	**Score** 1 very confident 10 not confident at all
Take a bath or shower	
Reach into cabinets or closets	
Walk around the house	
Prepare meals not requiring carrying heavy or hot objects	
Get in and out of bed	
Answer the door or telephone	
Get in and out of a chair	
Getting dressed and undressed	
Personal grooming (e.g., washing your face)	
Getting on and off of the toilet	
Total Score	

V. SUN EXPOSURE

1. How many times a week do you spend more than 10 minutes outside? _____
2. How much time do you spend outdoors (minutes) per week?_____
3. How much of your outdoor time is spent without sunscreen on (minutes)?_____
4. How much of your outdoor time is spent "fully exposed" (minutes)?_____
   ("fully exposed" is defined as uncovered face, arms, and hands)

VI. EXERCISE HABITS

1. How many times per week do you generally exercise? _____

   a. What type(s) of exercise do you generally perform? (circle all that apply)
   Walking Running Bicycling Swimming

Date: _____

Weight Lifting Aerobics Spinning Tennis

Other _____

b. In a typical week, how many days do you exercise ? (circle)

0-1 time/week 2-3 times/week 4-6 times/week daily

c. How many minutes do you typically exercise per session (circle)

<15 min 15-30 min 30-45 >45
Other_____

d. What is the typical level of exertion during your exercise?

Light Moderate Moderate/Heavy Heavy

e. When you are exercising do you ever feel limited by the following?

	Yes	No	Activity
Breathing	___	___	_____
Chest arm neck pain	___	___	_____
Low back pain	___	___	_____
Side ache	___	___	_____
Leg pain	___	___	_____
Foot drop	___	___	_____

Other? Please explain _____
_____

VII. MULTIPLE SCLEROSIS STATUS

1. How long have you been diagnosed with Multiple Sclerosis? _____
2. When did you have your first MS symptom? _____
3. Has your physician ever discussed what type of MS you have? **YES NO**

Relapsing remitting Primary progressive Secondary progressive Progressive relapsing

4. Briefly described your current MS symptoms _____
_____

Date: _____

5. Does MS affect your legs? **YES** **NO** Does MS affect your arms? **YES** **NO**

If yes, which leg is more involved? Right Left Both same
If yes, which arm is more involved? Right Left Both same

6. Do you feel numbness in your legs? **YES** **NO**

If yes, which leg is more involved? Right Left Both same

7. Do you feel numbness in your arms? **Yes** **No**

If yes, which arm is more involved? Right Left Both same

8. Do you feel tingling in your legs? **YES** **NO**

If yes, which leg is more involved? Right Left Both same

9. Do you feel tingling in your arms? **YES** **NO**

If yes, which arm is more involved Right Left Both same

10. Do you fatigue easily? **YES** **NO**
If yes, what causes it to be worse? _____
_____

11. Do you ever experience worsening of symptoms? **YES** **NO**

	Describe	**YES**	**NO**	**How often?**
Bath/shower	_____	____	____	_____
Physical activity	_____	____	____	_____
Hot outside	_____	____	____	_____
Other	_____	____	____	_____
Other	_____	____	____	

12. Do you drive yourself independently? **YES** **NO**

13. Do you walk (circle) without aid with cane walker wheelchair

14. Has your physician ever recommended that you get a bone scan?_____

15. Has your physician ever recommended that you exercise? _____

Family Practice Physician _____ Phone _____

Neurologist _____ Phone _____

Date: _____

Other _____ Phone _____

VIII. EMPLOYMENT STATUS

1. Full-time employed ____
2. Part-time employed ____
3. Retired ____
4. Not working ____

Please describe employment status _____
_____

IX. EDUCATION

1. None ____
2. High School ____
3. College ____
4. Masters ____
5. Ph.D. ____
6. Other ____

I certify that these answers are accurate and complete

_____ _____
YOUR SIGNATURE DATE

TABLE 13-3

Self-Administered Kurtzke

Instructions: Individuals with MS may experience difficulty in a number of different areas. For each of the 8 neurological categories below, please indicate the degree of difficulty (none, minimal, moderate, or severe) that you are experiencing at the present time.

	None	Minimal Difficulty Interferes only Slightly With Function	Moderate Difficulty Interferes Significantly With Function	Severe Difficulty Little or No Function Is Possible
1. Weakness in arm(s) and/or leg(s)	0	1	2	3
2. Tremor, clumsiness, or loss of balance	0	1	2	3
3. Double vision or slurred speech, or difficulty swallowing	0	1	2	3
4. Numbness or difficulty in feeling heat, pain or vibration in any part of the body	0	1	2	3
5. Frequency or urgent urination, awakening to urinate, not emptying the bladder completely, loss of bladder or bowel control, or constipation	0	1	2	3
6. Blurred vision in one or both eyes (even with glasses)	0	1	2	3
7. Difficulty with memory, calculation or reasoning	0	1	2	3
8. Stiffness or jerking of the muscles	0	1	2	3

OVERALL FUNCTION

On the following two pages are a number of statements that might be used to describe the overall function of MS subjects. These statements are arranged in order from least severe (0) to most severe (9.0).

Instructions:

1. First, locate the item that best describes your ability to walk.
   - If you are able to walk without limitations, please choose a statement under the section called "Able to Walk."
   - If you are able to walk only a limited distance, please choose a statement under the section called "Able to Walk Only a Limited Distance."
   - If you require aid(s) or assistance to walk or are unable to walk, please choose a statement under the section called "Aid(s) Required or Unable to Walk."
2. Circle the number of the one statement which best describes your overall condition at the present time.
3. In selecting your answer, refer back to your rating of the 8 neurologic categories listed.

Remember: Choose on *one* of the statements (0-9.0) which follow.

ABLE TO WALK

0.0 Essentially normal
1.0 Abnormality in *one* of the neurological categories but with no difficulty in function
1.5 Abnormality in *more* than one of the neurological categories but with no difficulty in function
2.0 Minimal difficulty in one of the neurological categories
2.5 Minimal difficulty in two of the neurological categories
3.0 Moderate difficulty in one of the neurological categories, able to walk
3.5 Moderate difficulty in one of the neurological categories and minimal difficulty in *one or more* of the neurological categories, able to walk

ABLE TO WALK ONLY A LIMITED DISTANCE

4.0 Able to walk without aid or rest at least 7 city blocks (500 meters or 1,625 feet)
Self-sufficient, up and about some 12 hours a day (Relatively severe difficulty in one neurological category or moderate difficulty in several of the neurological categories)

4.5 Able to walk without aid or rest at least 4 city blocks (300 meters or 975 feet)
May need minimal assistance, able to work a full day but may have some limitation of full activity
(Relatively severe difficulty in one neurological category or moderate difficulty in several of the neurological categories)

5.0 Able to walk without aid or rest at least 2 ½ city blocks (200 meters or 650 feet)
Disability is severe enough to limit full daily activities—for example: to work a full day without job modifications
(Very severe difficulty in one of the neurological categories)

5.5 Able to walk without aid or rest at least 1 city block (200 meters or 325 feet)
Disability is severe enough to prevent full daily activities
(Very severe difficulty in one of the neurological categories or moderate difficulty in several of the neurological categories)

AID(S) REQUIRED OR UNABLE TO WALK

6.0 Assistance on *one* side (cane, crutch, brace) is required to walk approximately 1 city block (approximately 100 meters or 325 feet), with or without resting

6.5 Constant assistance on both sides (canes, crutches, braces, walker) is required to walk about 20 meters (65 feet)
(Moderate difficulty in more than two neurological categories)

7.0 Unable to walk more than about 5 meters (16 feet) even with aid
Essentially restricted to wheelchair
Can wheel self in standard wheelchair and can transfer alone
Up and about in wheelchair some 12 hours a day
(Severe difficulty in more than one neurological category or severe weakness only)

7.5 Unable to take more than a few steps, restricted to wheelchair
Can wheel self in standard wheelchair and may need aid to transfer
Cannot remain in wheelchair for a full day
May require motorized wheelchair
(Severe difficulty in more than one neurological category)

8.0 Essentially restricted to bed or chair
Propelled by others in wheelchair
May be out of bed part of the day
Can use arms and able to care for self
(Severe difficulty in several neurological categories)

8.5 Essentially restricted to bed much of the day
Has limited use of arms
Retains some self-care functions
(Severe difficulty in several neurological categories)

9.0 Restricted to bed
Cannot use arms
Can speak, can eat if fed by others
(Severe difficulty in several neurological categories)

Source: Scheinberg, L.C. Medical Rehabilitation Research and Training Center for MS, Department of Neurology, Albert Einstein College of Medical, Bronx, New York.

TABLE 13-4
Self-Administered Kurtzke (French Version)

Symptoms	NONE	MILD	MODERATE	SEVERE
1. Weakness of right arm	0	1	2	3
2. Weakness of left arm	0	1	2	3
3. Weakness of right leg	0	1	2	3
4. Weakness of left leg	0	1	2	3
5. Leg stiffness or deficit at walk	0	1	2	3
6. Tremor	0	1	2	3
7. Clumsiness of arms	0	1	2	3
8. Lose of balance	0	1	2	3
9. Double vision	0	1	2	3
10. Difficulty in speaking and/or swallowing	0	1	2	3
11. Uncontrolled urinary urgency	0	1	2	3
12. Difficulty in urination, incomplete micturition Or bladder emptying	0	1	2	3
13. Constipation	0	1	2	3
14. Loss of control of bladder	0	1	2	3
15. Loss of control of bowel	0	1	2	3
16. Difficulty in feeling a contact	0	1	2	3
17. Difficulty in feeling heat	0	1	2	3
18. Difficulty in feeling pain	0	1	2	3
19. Pain or burning sensation in any part of the body	0	1	2	3
20. Bizarre feeling (pins or needles, constriction) in any part of the body	0	1	2	3
21. Difficulty with memory	0	1	2	3
22. Difficulty with calculations	0	1	2	3
23. Difficulty with reasoning or thinking	0	1	2	3
Level of vision (with glasses)	>7/10 (reading possible)	6/10-4/10 (recognition possible)	3/10 or 2/10 (distinction of forms)	<1/10 (loss of vision)
24. Right eye	0	1	2	3
25. Left eye	0	1	2	3

Source: Verdier-Taillefer MH, Rouiiet E. Cesaro P. Alperovitch A. Validation of self-reported neurological disability in multiple sclerosis. *International Journal of Epidemiology* 1994; 23: 148-154.