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RELATIONSHIP BETWEEN SOLEUS H – REFLEX AND BALANCE METRICS IN PEOPLE WITH MULTIPLE SCLEROSIS

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GREGORY SCOTT CANTRELL
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RELATIONSHIP BETWEEN SOLEUS H – REFLEX AND BALANCE METRICS IN PEOPLE WITH MULTIPLE SCLEROSIS

A DISSERTATION APPROVED FOR THE
DEPARTMENT OF HEALTH AND EXERCISE SCIENCE

BY

_____
Dr. Rebecca Larson, Chair

_____
Dr. Michael Bemben

_____
Dr. Christopher Black

_____
Dr. Daniel Larson

_____
Dr. Lee Williams

Dedication

To my beautiful and most-supportive wife, Rachel.

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I would like to take a second and recognize the work of my committee members Drs. Larson, Bemben, Black, Williams, and the late Dr. Beck. Without their time and insight this project would not have been completed to the extent that it was. From the moment I stepped onto OU's campus and more specifically joined the Health and Exercise department I immediately felt accepted and a part of the OU family. I am extremely grateful for every opportunity afforded to me over the last four years, and will hopefully make each of you proud as I begin my journey in academia.

Table of Contents

List of Tables

List of Figures

Abstract

Multiple sclerosis (MS) is a chronic immune-mediated disease that wreaks havoc on the central nervous system (CNS). The disease attacks and degrades the myelin sheath that insulates axons in the CNS, as well as the cells that generate myelin known as oligodendrocytes. In chronic cases it can even transect the axons themselves. The degradation leads to impaired conduction of electrical signals that travel to and from the CNS. Due to the variability in degradation sites symptoms associated with MS differ considerably from person to person. However, common symptoms consist of muscle weakness, fatigue, and impaired mobility and balance. Recently, the notion of bilateral asymmetry has become more commonplace in MS research, and has been observed in many physiological variables, such as aerobic capacity, muscular strength and power, as well as skeletal loading. Yet, one area that has not been investigated involves spinal reflexes, particularly the soleus Hoffmann (H) reflex. Of importance, bilateral coordination reflexes between legs is necessary for tasks such as balance. PURPOSE: Therefore, the intent of this investigation was two-fold. First, to determine if the soleus H reflex was asymmetrical in a sample of people with MS; and secondly, is the asymmetry associated with impaired balance. METHODS: Eight volunteers with MS (Females = 5) and eight healthy volunteers (Females = 6) matched for age- and physical activity participated in this investigation. The MS patients had an average expanded disability status score of 3.1 ± 2.2 (median = 2, range = 1 to 6) indicating mild to moderate disability. The study consisted of six visits, five of which were for soleus reflex testing, one for balance testing, and the initial for necessary paperwork and familiarization to all experimental protocols.

Electrical activity of the soleus muscle was recorded using electromyography electrodes placed over the soleus muscle. To contract the soleus muscle involuntarily (the muscle was in a resting state) a stimulating electrode was placed over the tibial nerve located on the posterior aspect of the knee in the popliteal fossa, and another placed just proximal to the patella. Electrical stimulation started at ~ 0.5 volts and increased by 0.25V every seven to ten seconds until the H reflex reached a peak (H_{max}) and the direct muscle response (M wave) reached a plateau (M_{max}). EMG tracings were analyzed to determine H_{max} and M_{max} in order to standardize the H_{max} to the M_{max}. Each leg was tested twice in random order, but only once per visit. To increase reliability in day-to-day variability stimulating and recording sites were traced with a permanent marker, and stimulation visits were scheduled for the same time. Within-limb H_{max} / M_{max} ratios were compared using paired t-tests. Both left and right leg H_{max} / M_{max} ratios were averaged and compared using independent t-tests. After averaging each leg an asymmetry score was calculated and compared between groups using independent t-tests. The asymmetry score was then correlated to balance performance collected using dynamic dual-force plates. Two balance tests were used: the sensory organization test (SOT) and limits of stability (LOS) test. Body composition was assessed with dual-energy x-ray absorptiometry (DXA). RESULTS: Within-limb H_{max} / M_{max} ratios were similar for both legs in the MS group ($p > 0.05$). Left leg within-limb H_{max} / M_{max} ratios were similar in the left leg ($p > 0.05$) but differed in the right leg ($p < 0.05$). When each leg was averaged together and compared no significant between leg differences were observed for either group ($p > 0.05$). When the averaged H_{max} / M_{max} ratios were converted into an asymmetry

score a significant difference was observed between groups ($p < 0.01$), with the MS groups having a greater asymmetry score than the non-MS group. Asymmetry scores from each group were pooled and ran against the results from the SOT and LOS tests. Significant negative correlations were observed for condition four of the SOT and endpoint excursion, maximum excursion, and directional control from the LOS test in the forward direction (i.e., leaning forward). One significant positive correlation was observed between the pooled asymmetry scores and reaction time from the LOS test, also in the forward direction. No other significant correlations were observed between the asymmetry scores and the other conditions or the composite score of the SOT, or the other directions tested from the LOS test. Total body fat-mass and percent fat differed between groups ($p < 0.05$). No differences were observed in lower-leg composition results ($p < 0.05$). CONCLUSION: The results from this investigation further highlight the presence of bilateral asymmetries in MS patients, and that the soleus H reflex is significantly associated with many aspects of leaning forward. Of interest, is all asymmetries previously reported in the literature have required physical effort and/or motivation; however, the asymmetry observed in this investigation occurred in a resting muscle, which did not incorporate descending drive or require voluntary effort.

CHAPTER I: INTRODUCTION

Multiple sclerosis (MS) is a multifactor, immune-mediated disease affecting the central nervous system (CNS) in approximately 2.5 million individuals worldwide (65). Females are on average affected to a greater extent than their male counterparts, which has been estimated to be approximately 3:1 (7, 34). On average, diagnosis occurs in the third or fourth decade of life, and the disease prevalence varies considerably with North America and Europe affected to a greater extent (e.g., >100/100,000 inhabitants) than Eastern Asia and sub – Saharan Africa (e.g., 2/100,000) (34). While the etiology of MS remains unclear three influencing factors have been identified, which include genetic predisposition, environmental factors, and prior exposure to infectious agents such as Epstein-Barr virus (67). Common symptoms of MS include, but are not limited to, reduced strength, symptomatic fatigue, and balance and coordination deficits (10).

In 1996 Lubin and Reingold provided the medical and research communities with standardized definitions of the four identified types of MS (36, 37), consisting of 1) relapsing-remitting MS (RRMS), 2) primary progressive MS (PPMS), 3) secondary progressive MS (SPMS), and 4) progressive relapsing MS (PRMS) (35). Approximately 85% of MS patients are diagnosed as RRMS, which is characterized by frequent, reoccurring attacks with varying periods of remission separating the attacks (35, 65). Over time the majority of individuals initially diagnosed with RRMS will transition into SPMS (65), which is characterized as a reduction in attacks and the onset of gradual neurologic disability (65).

The pathogenic cascade of MS is initiated by abnormal behavior within the immune system in the peripheral circulatory system, such that specific cells (i.e., T cells) are "primed" to target, and subsequently degrade specific proteins and phospholipids of the CNS. Once primed, T-cells infiltrate a compromised blood-brain barrier (BBB), which is made up of layers of specialized cells that function to maintain the integrity of the cerebral spinal fluid within in the CNS, and initiate a series of cellular responses that end with the degradation of myelin as well as the cells responsible for generating new myelin, oligodendrocytes. The main driving force of the degradation appears to be inflammation (65). Indeed, myelin degradation and symptoms enter a state of remission once inflammation is no longer present (67).

The degradation of myelin negatively impacts saltatory conduction velocity, which is the propagation of an action potential along a myelinated axon (38). It is important to note that myelin is not a continuous structure, but rather interrupted at regular intervals known as nodes of Ranvier (38). Action potentials only propagate down the axon at the nodes of Ranvier, which increases the conduction velocity at which the action potential travels relative to an unmyelinated axon. In [genetically susceptible] people diagnosed with MS the immune system targets and degrades the myelin impairing, and potentially blocking in severe cases, the conduction of action potentials generated in the CNS out to a α-motor neuron (MN). Based on the pathophysiology of MS, it seems reasonable that electrical measures of muscle activation (e.g., electromyography, EMG) would be affected. Indeed, Scott et al. recently provided evidence of reduced EMG root mean square (RMS), a measure of EMG signal power, of the knee extensors at isometric contraction intensities greater

than 60% in a sample of MS patients; this was attributed to a reduction in motor unit firing rates (9, 53).

The Hoffmann (H) reflex, named after Paul Hoffmann – a German physiologist, was first described in 1910 (16), and later given its name "Hoffmann reflex" in 1950 by Magladery and McDougal (39). Hoffmann originally described two phases of the reflex arc, a direct muscle response of short latency (3-5 milliseconds, ms) and an indirect response of relatively longer latency (30-40 ms), known as the M – wave and H – reflex, respectively (21). The H – reflex is the electrical analogue to the classical monosynaptic stretch reflex, and has been used to assess motor unit excitability (21, 46, 59). Low levels of electrical stimulation applied to a peripheral nerve (e.g., tibial nerve) depolarize the large diameter sensory Ia afferent neurons that synapse onto an α-MN at the spinal cord which, if reaches threshold for depolarization, sends an action potential to its homonymous muscle fibers eliciting a muscle twitch that can be observed through EMG recordings (49). However, since the threshold to directly depolarize a α-MN is greater than that of sensory Ia afferents the M – wave will not be observed initially (46). However, as the electrical stimulus continues to increase the H – reflex will eventually reach a peak (H_{max}) and the M – wave will begin to appear. Further increases in intensity will result in a reduced H – reflex amplitude as the orthodromic afferent action potential collides with an antidromic efferent action potential generated in the α-MN. At supra-maximal intensities the H – reflex will be completely absent (21, 46, 59), and M – wave amplitude will eventually reach a plateau (M_{max}).

The soleus H – reflex is one of the most commonly studied reflexes in spinal excitability investigations due to the convenient accessibility of the tibial nerve (59, 66). Of importance, the soleus musculature is fundamental in maintaining proper posture, and modulation of the soleus H reflex is paramount during dynamic balancing tasks of differing difficulty on a wobble board (20).

Interestingly, when both sides of the body are measured independently MS has been shown to affect one side of the body to a greater extent than the other. This unique disparity between limbs has been reported in leg strength (29, 30), bone mineral density (28), peak oxygen consumption (68), knee extensor power (5), as well as metabolic processes such as glucose uptake during walking (58), and can introduce significant predicaments in a person's daily life [if not addressed]. Indeed, Chung et al. (2008) demonstrated knee extensor power was significantly associated with impaired postural control in a sample of MS subjects, and reported significant, positive correlation coefficients between knee extensor power asymmetry scores and normal and brisk walk times (5), indicating as the asymmetry in knee extensor power between limbs increased a greater amount of time was required to walk a prescribed distance. Moreover, measures of anterior / posterior (A/P) center of pressure (COP) as well as medial / lateral (M/L) COP were significantly correlated with loading asymmetry scores defined as the bilateral distribution of body mass with respect to limb preference during quiet standing (5). Huisinga et al. (17) recently reported MS patients had a significantly altered COP sway variability during quiet stance. This difference was observed in both frontal plane and sagittal plane sway, and was exacerbated with eyes closed.

Proper maintenance of postural control depends on the bilateral integration of somatosensory, visual, vestibular, and motor processes (4), most of which are frequently effected in people with MS (13). Indeed, impaired postural control is a common trait in people with MS (5, 19, 57). For example, Sosnoff et al. observed significant differences in medial-lateral sway range between MS subjects clustered into low and high spasticity groups and healthy controls (i.e., control < low < high) (63). Taken together, the observations of Sosnoff et al. (63) in addition to those of Chung et al. (5) highlight the importance of better understanding how asymmetry influences the ability to successfully accomplish functional tasks in MS patients such as maintaining proper balance, which impacts one's quality of life.

Purpose

Based on the importance of bilateral coordination of reflexes in maintaining balance, which tends to be impaired in MS patients, and evidence demonstrating the presence of bilateral asymmetries in people with MS that significantly impact activities of daily living and quality of life it was the intent of this investigation to 1) determine if bilateral asymmetry exists in the soleus H reflex in a sample of MS subjects; and 2) determine if this asymmetry differs from healthy age- physical activity matched participants without MS; and 3) determine if there is any relationship between the soleus H reflex asymmetry and balance.

Research Questions

1. Will soleus H_{max} / M_{max} ratio differ between limbs in a sample of MS subjects and healthy controls?
    1. Will asymmetry in H_{max} / M_{max} be greater in MS subjects?

2. Will the soleus H_{max} / M_{max} ratio be related to balance performance?

Hypotheses

1. Soleus H_{max} / M_{max} will differ significantly between limbs in MS subjects, and will differ minimally between limbs in Non-MS participants.
    1. H_{max} / M_{max} asymmetry scores will be greater in MS subjects.
2. Soleus H_{max} / M_{max} will be significantly negatively related to all SOT conditions and LOS test performance variables with the exception of reaction time.

Research Sub – Questions

1. Will SOT performance metrics differ between a sample of MS patients and Non-MS participants?
2. Will LOS test performance differ between a sample of MS patients and Non-MS participants?

Research Sub – Hypotheses

1. MS subjects will perform significantly worse than Non-MS participants in all six conditions of the SOT.
2. MS subjects will perform significantly worse than Non-MS participants in the four cardinal directions associated with the LOS test.

Significance

Spinal reflexes are known to play an integral part in bilateral processes such as maintaining postural control and MS patients have been shown to experience impaired postural control, which can significantly increase the risk for falling and living a more sedentary life. In addition, evidence exists demonstrating asymmetry in

disease in MS subjects, yet no study currently exist that examined the soleus H – reflex between legs in a sample of MS patients to determine if asymmetries in spinal excitability exist, and how bilateral asymmetries in the soleus H reflex relate to balance. Therefore, the results of this study will help explain how potential differences in the soleus H reflex between legs relate to balance in people with MS, and help guide future interventions.

Assumptions

The following are assumptions associated with the present study.

1. H – reflex derives solely from group Ia afferents that project mono-synaptically to α – motor neurons.
2. Participants will give maximal effort for all muscular fitness testing and functional testing.
3. Participants will provide accurate medical information and health history.
4. All participants will be honest when filling out fatigue questionnaires.
5. Participants complied with the directions and guidelines provided prior to testing. This includes refraining from exercise, caffeine, and food.

Delimitations

1. The findings of the study will only be applicable to healthy individuals and people diagnosed with multiple sclerosis between the ages of 20 and 65.
2. Multiple sclerosis patients will have neurologist confirmed diagnosis of relapsing-remitting multiple sclerosis (RRMS), and an extended disability status scale score (EDSS) less than 6.5.

3. The findings of this study will only be applicable to the soleus muscle.
4. Multiple sclerosis patients will be free from relapse for a minimum of 3 months.
5. Multiple sclerosis patients must not currently be using prednisone or other steroids for disease exacerbation within 3 months of the study
6. Individuals must not have asymmetric orthopedic limitations.
7. Individuals must not have multiple risk factors for cardiovascular diseases.

Limitations

1. The participants were willing volunteers from the Norman, OK and Oklahoma City, OK areas and will not represent a true random sample.
2. Because testing will occur on multiple testing visits, and fatigue is variable and unpredictable in MS patients, initial fatigue in MS patients may differ between testing visits.
3. Medications, symptom management, and disease modification will vary between MS patients.
4. Results will not apply to MS patients that have an EDSS score ≥ 6.5 or an MS diagnosis other than relapsing-remitting.
5. The control group will be matched with the MS group in age, gender, and physical activity.

Operational Definitions

1. Action potential – electrical neural impulse (38).
2. Antidromic volley– a volley of electric activity travelling in the wrong direction in a motor axon (39, 46).

3. Axon – part of motoneuron that transmits the result of an incoming message out to skeletal muscle in form of action potential (38).
4. Bilateral asymmetry – differences between sides of the body (29).
5. Center of gravity (COG) – a point in which all the mass of an object may be considered to be concentrated with respect to the pull of gravity. In normal subject standing erect, the center of gravity is located in the lower abdominal region and slightly forward of ankle joints (Neurocom International Inc.).
6. COG sway angle (θ) – the angle between a vertical line projecting upward from the center of the area of foot support and a second line projecting from that same point to a subject's COG (Neurocom International Inc.).
7. Central drive – descending neural output from supra-spinal centers to skeletal muscle.
8. Dendrite – part of motoneuron that receives signals from other neurons (38).
9. Directional control – a comparison of the amount of movement in the intended direction towards the target to the amount of extraneous movement away from target.
10. Electromyography (EMG) – a technique analogous to electrocardiography used to monitor skeletal muscle activation. Can be recorded within (intramuscularly) or on noninvasively on the surface of the skin (38).
11. Endpoint excursion – the distance of the first movement toward the designated target, expressed as a percentage of maximum LOS distance. The endpoint is considered to be the point at which the initial movement towards the target ceases.

12. Hoffmann (H) reflex – is a spinal reflex analogous to the muscle stretch reflex that depends on electrical stimulation rather than a mechanically elicited stretch for activation, allowing for the bypass of muscle spindle activity and subsequent γ –activation of intrafusal fibers (21, 59).
13. Interpolated twitch technique – the act of applying a single (or double) maximal stimulus to a motor nerve during a maximal voluntary contraction to assess level of muscle activation (38).
14. Kin Com Dynamometer – an electro-mechanical device used to provide resistance during isokinetic and isometric muscular contractions. This device will provide force and torque measurements during the different fatiguing exercise protocols.
15. Kurtzke Expanded Disability Status Scale (EDSS) – An incremental numerical scale from 1 – 10 used to assess the disability level of an individual with MS (26).
16. Limits of stability (LOS) – The maximum anterior, posterior, and lateral sway angles achievable without a fall, stumble, or reaching out. When the sway angle exceeds the LOS the subject must step, stumble, or grasp an external object to regain equilibrium (Neurocom International Inc.).
17. M – wave – a direct motor response [of shorter latency] as a result of electrical stimulation of a motor axon (21).
18. Maximal excursion – maximum distance achieved during the trial.
19. Maximal M – wave (M_{max}) – evoked by the recruitment of all motor axons, and provides an estimate of response provided by the whole MN pool (49).

20. Motor neuron – consists of a soma (cell body), and specialized processes known as dendrites and axon (38).
21. Motor unit – a single motor neuron and the fibers to which its axon runs (38).
22. Movement velocity – the average speed of COG movement measured in degrees per second.
23. Multiple sclerosis (MS) – an immune-mediated inflammatory disease of the central nervous system (CNS) (National MS Society).
24. Muscle spindle – sensory organs that monitor the length of a muscle, as well as the rate of change in length of a muscle (38).
25. Orthodromic volley – a volley of electric activity travelling in the correct direction in a motor axon (46).
26. Reaction time – the time in seconds between the command to move and the patient's first movement.
27. Relapsing remitting MS (RRMS) – a type of MS described by clearly defined disease relapses with periods of full or residual deficit upon recovery; periods of remission are characterized by a lack of disease progression (National MS Society).
28. Primary progressive MS (PPMS) – a type of MS characterized by worsening of neurologic function from the onset of symptoms, without early relapses or remissions (National MS Society).
29. Sensory organization test – a test that objectively identifies abnormalities in a patient's use of the three sensory systems that contribute to postural control (Neurocom International Inc.).

30. Spasticity – an inappropriate, velocity dependent, increase in muscle tonic stretch reflexes, due to the amplified reactivity of motor segments to sensory input. It is one component of the upper motor neuron syndrome and can lead to muscle stiffness and disability (15).

CHAPTER II: REVIEW OF LITERATURE

The follow review of literature will be presented as a series of individual analyses in a study-by-study manner. In brief, this review of literature will begin with an introduction into the disease multiple sclerosis (MS), and then describe in detail the pathophysiology of MS, then present some evidence demonstrating bilateral asymmetries will be presented, followed by a detailed analysis of the Hoffmann (H) reflex. Finally, this chapter will conclude by describing how bilateral asymmetries in the soleus H – reflex may contribute to postural impairments in MS patients.

Pathogenesis, Diagnosis, and Disease Course

Multiple sclerosis is a chronic disease affecting the CNS, and has been reported to reduce a patient's lifespan by seven to eight years on average; 50% of patients will not be capable of performing household and employment responsibilities ten years after disease onset and will be classified as non-ambulatory 25 years after disease onset (65). Multiple sclerosis has been referred to as a prototype of non-traumatic immune-mediated neurological dysfunction (65). The disease is complex and has four primary types of classification including relapsing-remitting MS (RRMS), primary progressive MS, secondary progressive MS, and progressive-relapsing MS (36). Risk factors have been identified such as genetic predisposition, environmental exposures known to affect the immune system including Epstein – Barr virus, smoking, and vitamin D deficiencies (52, 67), yet the etiology remains unclear; the pathology and pathophysiology of the disease have been extensively reviewed (31, 33, 47, 65, 67).

Focal areas of inflammation mediate the deterioration of myelin in brain and spinal cord tissue (32), while sparing the peripheral nervous system (14). The loss of

myelin impairs propagation of action potentials through sites of degeneration, which subsequently leads to neurological deficits and associated symptoms (14). Diagnostically, focal plaques of demyelination are considered the hallmark of MS pathology, and have been observed in both grey and white matter in the brain (32).

Inflammation is first triggered in the peripheral circulatory system where CD4 T – cells become primed and infiltrate the CNS via the blood – brain barrier (67). Once inside these cells identify specific proteins associated with the myelin sheath, release cytokines, and activate macrophages and B – cells that trigger local inflammation and results in demyelination of axons and destruction of the cells that synthesize new myelin, oligodendrocytes (67). Over time, inflammation will decrease and some myelin will regenerate. However, if demyelination is severe enough or present for an extended period of time the underlying axons will be damaged eventually leading to axonal degeneration and brain atrophy (65, 67). Symptoms vary between patients depending on lesion site(s), however, common symptoms include generalized muscle weakness and postural instability (14), which will be discussed in greater detail in sections to follow.

Over the past 4 decades the criteria for diagnosing MS has evolved paralleled with evolving medical technology (e.g., MRI) and various disease modifying therapeutic agents. In 1976 Rose et al. (56) provided the clinical community with early criteria to be used in establishing a diagnosis of MS. Approximately six years later Poser and colleagues convened in Washington D.C. with the intention of improving diagnostic criteria by reducing subjectivity in diagnosing MS and providing more objective MS criteria through incorporating laboratory, neurophysiological, neuropsychological, and neuroimaging procedures (50).

Poser et al., 1983 (50)

The intent of this two day workshop held in Washington D.C. in 1982 was to develop more objective MS diagnostic criteria by incorporating new reliable and valid ancillary procedures in order to conduct more effective therapeutic trials in multicenter programs, to compare epidemiological surveys, to evaluate new diagnostic criteria, and to estimate the activity of disease process in MS.

A few important and useful concepts were defined, including *attack, clinical and para-clinical evidence of a lesion, remission, and laboratory* support. Because these concepts are used throughout the rest of their review, summarized definitions will be provided.

1. Attack – also referred to as a bout, episode, or exacerbation. The occurrence of a symptom or symptoms of neurological dysfunction, with or without objective confirmation, and lasts greater than 24 hours.
2. Clinical evidence of a lesion – signs of neurological dysfunction observed by neurological examination.
3. Para-clinical evidence of a lesion – the demonstration of a lesion of the CNS that has not yet produced signs of dysfunction, and may or may not have caused symptoms in the past.
4. Remission – a definite improvement in signs, symptoms, or both that persists for at least 24 hours. A remission lasting more than one month is considered significant.
5. Laboratory support – applies to examination of cerebral spinal fluid for oligoclonal bands and increased production of immunoglobulin G (IgG).

In addition to diagnostic definitions, two major classification groups were proposed, consisting of *definite* and *probable*, which were then further divided into *clinical* or *laboratory-supported* MS.

Clinical definite MS (CDMS) was described by presenting with two attacks and clinical evidence indicating two distinct lesions, or two attacks with one clinically evident lesion plus one para-clinical evidence of a second separate lesion. Laboratory-supported definite MS (LSDMS) was described as evidence of IgG oligoclonal bands (OB), indicators of inflammation, in the CSF or an increased production of IgG by the CNS, in addition to two attacks in two distinct sites of the CNS separated by at least one month. Clinically probable MS (CPMS) is described as suffering two attacks and clinical evidence of one lesion; whereas, laboratory-supported probable MS (LSPMS) was described as suffering two attacks and presence of OB/IgG in CSF. Congruent with CDMS and LSDMS the attacks described in CPMS and LSPMS must be at least one month apart, last greater than 24 hours, and involve two separate sites of the CNS.

Overall, these authors developed more objective diagnostic criteria by expanding on the earlier Schumacher criteria in order to identify groups of patients whose diagnosis would be accepted worldwide, and allow for greater participation in various clinical studies.

Lubin and Reingold, 1996 (36)

Concerned with improving communication and understandings between clinicians and researchers, Lubin and Reingold summarized results of an international survey and proposed standardized definitions for the different clinical courses of MS.

Relapsing-remitting MS (RRMS), the most common clinical course comprising approximately 85% of patients (65), was defined as clear and definite disease relapses (see Poser et al. for definition of relapse) with either full recovery or with *some* degree of residual upon recovery; the defining feature of RRMS being transient bouts of worsening neurologic function with periods of variable amounts of recovery.

Three types of *progressive* MS have been defined. A diagnosis of primary progressive MS (PPMS) requires gradual worsening of neurologic function and no clearly distinct relapses. However, it was recognized that continuous decline at a constant rate was unlikely, and therefore, small variations in the rate of disease progression over time must be considered in the definition. Secondary-progressive MS (SPMS) was defined as being initially RRMS indicated by episodic periods of attacks and subsequent recovery that progressed into continuous decline in function without clearly defined relapses, periods of remission, and plateaus in disease progression.

Kurtzke, 1983 (26)

In 1983 Dr. John Kurtzke expanded upon his original Disability Status Scale (1955) designed to evaluate the treatment effects of isoniazid in what became known as the Expanded Disability Status Scale (EDSS)(26). Originally the scale was used to evaluate the degree, or magnitude, of neurologic dysfunction based on a neurologic examination in MS patients by grading 8 “functional systems” (FS) on a scale ranging from 0 (normal) to 5 or 6 (maximal impairment), in addition to an overall disability scale ranging from 0 (normal) to 10 (death by MS); an overall score of 6 indicates the dependence on *some* unilateral walking aid (e.g., cane).

Function was measured in eight "mutually exclusive" groups consisting of Pyramidal, Cerebellar, Brain Stem, Sensory, Bowel and Bladder, Visual, Cerebral, and Other. Pyramidal, Cerebellar, Sensory, and Bladder and Bowel refer to physical impairments manifesting below the head, regardless of lesion site, while Brain Stem functions are related to both supraspinal and inter-segmental neural tracts. The expansion of the DSS, which included the addition of half steps within the original 0 to 10 scale, was to provide greater sensitivity in the scale for research interested in monitoring changes over time in chronic MS; this suggestion was made by researchers who thought the middle section of the scale lacked sensitivity to appropriately detect change. A gain or loss of 0.5 in the EDSS score will define better or worse respectively. The 19 steps of the EDSS consist of:

1. EDSS 1.0 – limited to one FS with a grade of 1, excluding cerebral grade 1, which includes mood aberrations, and all others with a grade of 0.
2. EDSS 1.5 – limited to two or more FS with a grade of 1, but nothing greater than 1.
3. EDSS 2.0 – limited to one FS with a grade of 2, all others with a grade of 0 to 1.
4. EDSS 2.5 – limited to two FS with a grade of 2, all others with a grade of 0 or 1.
5. EDSS 3.0 – limited to one FS with a grade of 3, or 3 or 4 FS with a grade of 2, and others with a grade of 0 to 1.

6. EDSS 3.5 – limited to one FS with a grade of 3 plus one or two with a grade of 2, or two FS with a grade of 3, or five FS with a grade of 2, and others with a grade of 0 to 1.
7. EDSS 4.0 – limited to combinations exceeding two FS with a grade of 3, or one grade 3 and two FS with a grade of 2, or five FS with a grade of 2, or one FS with a grade of 4, and others with a grade of 0 or 1. However, at this step the ability to walk, work, and complete daily activities takes precedence of the grades assigned to the FS. EDSS 4.0 requires ability to walk at least 500 meters without aid or rest, and to carry out activities of daily living including work of average physical difficulty.
8. EDSS 4.5 – limited to patients able to walk at least 300 meters without aid or rest, and complete work of average difficulty. The patient must be up most of the day with just limited activity.
9. EDSS 5.0 – limited to patients able to walk at least 200 meters without aid or rest, but disability is severe enough to limit a full day of activities.
10. EDSS 5.5 – limited to patients able to walk at least 100 meters without aid or rest, and requires special provisions to complete a ½ day of full (part-time).
11. EDSS 6.0 – limited to patients who require some form of aid while walking 100 meters. This form can be a cane, crutch, brace, or assistance of another individual.
12. EDSS 6.5 – limited to patients that require assistance to walk 20 meters; assistance is typically bilateral.

13. EDSS 7.0 – patient are restricted to a wheelchair for distances greater than 5 meters. The patient can still get around with chair on own, and remain up in the chair for 12 hours, and may be employed.
14. EDSS 7.5 – patient is unable to take more than a few steps and is restricted to a wheelchair. They can wheel around, but not for the entire day as in EDSS 7.0. The wheelchair may be motorized.
15. EDSS 8.0 – patients considered to be restricted to the bed, a chair, a passively in a wheelchair most of the day, but still retains ability to maintain self-care. Both arms retain function.
16. EDSS 8.5 – patient cannot tolerate full days in a chair, and is mostly restricted to the bed. Can still use one or both arms for self-care, but not to the extent in EDSS 8.0.
17. EDSS 9.0 – described as "helpless bed patients" that can still eat and communicate. They cannot perform self-care functions.
18. EDSS 9.5 – described as a completely helpless bed patient who cannot communicate effectively, eat, or swallow.
19. EDSS 10.0 – death caused by MS. This can be an acute event due to brainstem involvement or respiratory failure, or as a consequence of being bedridden. It excludes inter-current causes of death.

A more detailed explanation of each grade for all FS and each EDSS step can be found in the appendices A and B of Dr. Kurtzke's article (26).

McDonald et al., 2001 (40)

In 2001 an international panel of physicians, clinicians, and researchers presented revised diagnostic criteria recommendations for MS based on advancements in clinical technology (e.g., magnetic resonance imagery, MRI). The panel reviewed previously established definitions used in diagnostic criteria for the purpose of improving future diagnoses. For the purpose of effectively diagnosing MS, obtaining objective evidence demonstrating the expansion of lesions typical to MS in time and space is important. Moreover, anecdotal claims of symptoms is not enough to definitively diagnose MS, but can provide supporting evidence in the presence of lesions separated in time and space. When clinical presentation is not sufficient to make a diagnosis, laboratory test measures, such as MRI, analysis of cerebrospinal fluid (CSF), and visual evoked potentials can provide additional support for making a sound clinical diagnosis. It is important to objectively define subjective terminology considered in diagnosing MS. For instance, the term *abnormality* lies on a continuum and can present as mild to severe, and therefore requires further defining if an abnormality is to be accurately determined. Three important questions related to defining diagnostic criteria were clarified:

1. What constitutes an attack?
2. How is the time between attacks measured?
3. How is abnormality in para-clinical tests determined?

Pathophysiology of MS

MS can affect the body in many different ways depending on lesion site and whether or not a patient is currently in a state of remission or relapse. While symptoms

definitely vary among patients a few that are common, and poses a significant risk on a patient's quality of life (QOL) and their ability to perform functional activities of daily living (ADL), are generalized muscle weakness, muscle spasticity, and impaired balance or gait (57).

Maintaining proper balance requires the integration of multiple sensory systems including visual, vestibular, and somatosensory input (13). Unfortunately, these important systems are commonly impaired in MS patients, which increase their risk for falling. Indeed, a retrospective study published in 2002 that quantified fall risk among MS patients and important variables associated with falls reported 54% of MS patients included in analysis (n=27) had reported at least one fall over the previous two months (4). And, of those patients, 32% were classified as "recurrent fallers" as they reported having fallen at least twice. The Equiscale test for balance indicated a significant difference between the two groups (i.e., "fallers" and "non-fallers") in balance performance, with non-fallers scoring better than fallers (14.1±2.5 vs. 9.3±5.3) (4). The score of the Equiscale test is based on eight different conditions scored from 0 to 2; a score of 16 representing perfect balance (4). In a more recent cross-sectional descriptive study, 52.2% of study participants 45 to 90 years of age reported a fall in the prior six months (11), increasing the likelihood of sustaining an injury. In fact, more than 50% of 354 MS patients aged 55 to 94 reported at least one injurious fall over the prior six months (48). The results presented in these studies indicate a high prevalence of falls exists among people diagnosed with MS, and the need to address balance and postural strategies among MS patients.

Indeed, Huisinga et al. (17) reported postural control strategies during a simple quiet standing task were altered in 15 individuals diagnosed with MS (average EDSS: 4.5±1.8, median EDSS: 5.2) asked to stand quietly on a force platform for five minutes with eyes open or closed. Sway variability was quantified using the root mean square (RMS) calculated from the COP time series in both directions (i.e., anteroposterior, AP; mediolateral, ML). MS subjects had significantly greater sway area (mm^2; CON: 3.53±2.92 vs. MS: 12.23±9.14), as well as significantly greater median sway velocity (mm/s; CON: 0.98±0.56 vs. MS: 3.12±2.44). In the frontal (ML) and sagittal plane (AP), RMS was significantly greater in MS subjects, which was exacerbated during the eyes closed condition (17). While not measured in this study spasticity was suggested to be one factor resulting in the observed increased COG sway, as higher levels of spasticity are related to increased levels of COG sway (63).

Karst et al. measured COP movement in the sagittal plane (y) during two different conditions in 21 MS subjects (15 women; mean EDSS: 2.1±1.6; median: 2.0, range 0.0 – 6.0) and 21 age and gender matched controls (15 women); the tasks involved leaning and reaching (19). During the leaning task control subjects moved their COPy (i.e., anterior/posterior limits of stability) over a significantly greater distance than the MS group (cm; CON: 14.2±2.6 vs. MS: 11.9±2.9). Similarly, during reaching tasks the control group demonstrated significantly greater peak-to-peak COPy displacement, which was explained by a greater displacement in the positive direction (+) (19). A smaller COPy displacement was suggested to be either a voluntary or involuntary self-limiting strategy reducing the amount deviation from initial COP in the sagittal plane to reduce the likelihood of falling (19). Differences in peak-to-peak COP

displacement and COPy+ persisted even when comparing control subjects to 12 MS subjects with the highest Berg Balance Scale (BBS) scores (i.e., 55 or 56). It should be noted the secondary analysis is underpowered due to the reduced sample size, and therefore, the differences reported should be interpreted cautiously.

In 2008, Chung and colleagues calculated the net COP in both planes in 12 MS patients (PPMS = 1; RRMS = 6; SPMS = 4; Unclassified = 1) and 12 age-matched healthy controls (5). COP measurements were made during 20 seconds of quiet standing using dual force platforms. In contrast to the work of Karst and colleagues, Chung et al. (5) also calculated a bilateral distribution (i.e., loading) of body mass asymmetry score; a score of 100% indicated all body weight was supported on one foot, whereas a score of 0% indicated even distribution of body mass beneath the feet. A significant difference was observed for loading asymmetry (CON: 6.0±3.0% vs. MS: 10.5±6.9%) that indicated bilateral differences in ground reaction forces between feet. Additionally, mean AP COP variability was greater in the MS group (mm; CON: 4.33±1.79 vs. MS: 7.52±3.02), while ML COP variability tended to be greater in the MS patients (CON: 2.22±1.70 vs. MS: 4.15±3.10), but failed to reach significance (5). However, AP and ML COP variability were correlated with loading asymmetry indicating a reduced stability, and further confirming postural control is impaired in mild to moderate MS (5).

Spasticity is a commonly reported symptom associated with MS (54, 63), and has been defined as an inappropriate, velocity dependent, increase in muscle tonic stretch reflexes, as a consequence of augmented reactivity of motor segments to sensory input (15). An early 2000 report from the Patient Registry of North American Research

Committee on MS indicated 84% of MS patients reported some degree of spasticity, ranging from mild to severe. In a recent cross-sectional study examining 16 MS (2 males) and 16 age and gender matched controls Sosnoff et al. (63) clustered the MS group into low (n=7) and high spasticity (n=9) to determine how spasticity relates to postural control. Postural control was based on COP motion and was measured in the frontal and sagittal planes. Significant differences were identified in postural sway. Like expected, the high spasticity group demonstrated the greatest sway (238.9 mm^2) followed by the low spasticity group (100.9 mm^2) and controls (38.1 mm^2) (63). Moreover, the control group demonstrated a lower sway velocity than both MS groups (CON: 3.04 mm^2/s vs. H: 10.9 mm^2/s and L: 6.58 mm^2/s). Unlike Chung et al., no difference in AP sway range was observed between groups; however, significant differences in ML sway range were observed between the high spasticity group (10.28 mm) and the low spasticity group (6.59 mm) and controls (2.32 mm), with no statistical difference observed between low spasticity and controls.

Different ways exist in identifying or assessing spasticity; one common method involves the measuring the Hoffmann (H) reflex. Interestingly, modulation of the [soleus] H – reflex plays a vital role in static and dynamic postural control (3, 22, 23). The following section will introduce and describe the H – reflex followed by a review of literature that has examined the H – reflex and its influence on postural control metrics.

The Hoffmann reflex

The Hoffmann (H) reflex was first demonstrated by Piper (1912), but more clearly described in 1918 by Paul Hoffmann (16). However, it was not until 1950 that

Magladery and McDougal gave the reflex its official name (39). Hoffmann described two distinct responses at the muscle following percutaneous stimulation of the tibial nerve, a response of shorter latency and one of a longer latency. The shorter latency due to direct depolarization of motor axon and only observed with stimulation intensities greater than motor threshold, and the longer response due to depolarization of Ia afferent fibers whose origin is anchored onto muscle spindles, which synapses onto and depolarizes, once membrane potential reaches threshold, an α – motor neuron. The first response became known as the motor response, or M – wave, and the later response, the H – reflex. In healthy individuals the latency of the M – wave is ~ 6 – 9 milliseconds (ms), whereas the latency of the H – reflex is ~ 30 ms (46).

A benefit of using electrical stimulation to trigger a reflex rather than a mechanical stimulus, such as a reflex hammer, is electrical stimulation allows for the bypass of muscle spindle activity and its associated gamma motor neuron activity (21). However, despite this, the H – reflex is not a monosynaptic reflex as originally thought (39, 42); the Ia afferent volley can be influenced by other "large diameter" afferents contributing (i.e., oligosynaptic input) to the modulation of the H – reflex amplitude. The location of which can be nearby, as in an antagonist muscle (24), or distant, such as in a contralateral limb (6). Mechanisms that modulate H – reflex amplitude include presynaptic inhibition, post-activation depression, reciprocal inhibition, nonreciprocal inhibition, and recurrent inhibition(42). These factors can influence the amount of neurotransmitter released from afferent terminals into the synaptic cleft, the excitability of motor neurons, and can alter the intrinsic properties of the motor neuron (42).

Presynaptic inhibition has been observed in humans following the application of a conditioning stimulus to a heteronymous peripheral mixed nerve. For example, Iles and Robert (1987) demonstrated vibration applied to heteronymous muscles, both distant and antagonistic in function, resulted in some level of presynaptic inhibition (18). More specifically, vibration, operating at 100 Hz and timed to end 35 – 60 ms prior to each conditioned reflex, of the tibialis anterior significantly decreased the soleus H – reflex and vibration of the semitendinosus reduced the soleus H – reflex to a lesser extent (18). Moreover, Iles and Robert observed similar effects with the use of electrical stimulation applied to a peripheral nerve (18). Specifically, when the common peroneal nerve was stimulated with either a single or double shock at 300Hz a biphasic presynaptic inhibition was observed; the first phase lasting approximately 10 ms (reached peak decline around 2ms) and approximately 90 ms for the second phase with reductions of 25% and 20% respectively(18). With the addition of stimuli delivery (i.e., > 2 electrical pulses) the first phase of inhibition became non-existent, while the second phase became more pronounced, with an approximate 40% reduction in C/T amplitude. These results indicate the soleus H – reflex is sensitive to the activity of antagonistic afferents (18), and the level of activity in afferents may influence the magnitude of inhibition (24, 42).

Post-activation depression is a second way that H – reflex can be modulated(42). Instead of conditioning the reflex with either vibration or electrical stimulation applied to a peripheral nerve, post-activation depression involves recent activity occurring at the synapse of an Ia afferent and its homonymous α – MN. Ten years after Iles and Roberts and in contrast to their results, Kohn and colleagues (24) demonstrated conditioning of

soleus H – reflex with stimulation of the common peroneal nerve (CPN; activates tibialis anterior muscle) resulted in minimal presynaptic inhibition of the soleus H – reflex at latencies of one, two, and three seconds (24). However, when the soleus H – reflex was conditioned by stimulating the posterior tibial nerve (PTN; activates soleus muscle) subsequent test reflexes remained depressed at all three latency time intervals tested (i.e., 1, 2, and 3 seconds). With the use of transcranial magnetic stimulation Kohn and colleagues were able to exclude postsynaptic inhibition confirmed by no change in excitability of the motor neuron pool at the same latency time intervals tested. Based on the evidence, they concluded homosynaptic depression (or post-activation depression) localized at the Ia afferent terminal was the driving force for the attenuated soleus H – reflex (24). Unfortunately, the mechanism(s) explaining this depression remains unanswered; however, two potential options include reduced neurotransmitter release at the afferent terminal (21, 24), or an inactivation of calcium channels (42).

Based on this review of literature no research currently exists, specifically examining the soleus H reflex between legs, to investigate the potential for asymmetry in people with MS. Therefore, determining whether or not asymmetry in the soleus H – reflex exist in MS patients can help guide future therapies in addressing appropriate deficiencies related to the disease and the patient's ability to perform functional tasks such as balance with the goal to improve confidence and quality of life.

CHAPTER THREE: METHODOLOGY

Introduction

The following chapter will present the methodology for the current study which includes; a description of participants, their inclusion and elusion criteria, the design of the study, data collection procedures, instrumentation to be used, and how the data will be stored and analyzed.

Participants

Based on a power analysis using young vs. old H_{max} / M_{max} data from Koceja et al. (23) with an alpha level of 0.05, statistical power set to 0.80, and an effect size of 2.1 a total of 10 participants were required. A total of 17 volunteers between the ages of 20-64 years were recruited for participation in the present study. Eight participants were diagnosed by a board certified neurologist with either relapsing remitting or primary progressive multiple sclerosis and the other eight were healthy age- and physical activity-matched non-MS participants. Each participant was provided detailed information regarding the requirements of the study and provided verbal and written informed consent approved by the institutional review board at the University of Oklahoma before familiarization and data collection took place. All participants were also required to provide physician's clearance prior to enrollment. MS volunteers were recruited from Oklahoma Medical Research Foundation (Oklahoma City, OK), the Oklahoma City Veteran Affairs Hospital and surrounding areas of Norman, OK. MS participants also had to have an expanded disability severity scale (EDSS) score of less than 6.5, which indicates being able to walk a distance of 100 meters without aid or rest (27). Non-MS participants were recruited from the University of Oklahoma as well as surrounding areas of Norman, OK using flyers, emails, and word of mouth.

Inclusion criteria

Individuals meeting the following criteria were considered for participation in the current study.

1. Individuals between the years 20 and 64.
2. Individuals currently not smoking or quit at least six months ago.
3. Individuals must have physician's diagnosis of *relapsing-remitting multiple sclerosis*, and free from relapse during the previous three months. A relapse is defined as a worsening of symptoms maintained for at least 24 hours and has been prescribed steroids. (Does not apply to control subjects)
4. Individuals with written physician's clearance.
5. Individuals with an EDSS score of < 6.5, which indicates being able to walk at least 100 meters without aid or rest.
6. Individuals not taking prednisone or other steroids medications.
7. Individuals willing to not take medications to manage symptoms of spasticity on test days.

Exclusion criteria

Individuals presenting with any of these criteria will not be considered for participation.

1. Individuals outside of 20 to 64 years of age.
2. Smokers.
3. Individuals diagnosed with secondary progressive MS (Does not apply to control subjects).
4. Individuals without written physician's clearance.

5. Individuals with an EDSS score ≥ 6.5 indicating either aid or rest is required to walk 100 meters.
6. Individuals currently taking prednisone or other steroids for management of symptoms.
7. Individuals taking medication to manage symptoms of spasticity on test days.

Experimental design

The present study was a randomized, cross-sectional, repeated measures design comparing a sample of RRMS or PPMS subjects and healthy controls. The study required each participant to visit the Human Performance Laboratory a total of six times, which included one visit for completion of all appropriate documents and familiarization of procedures and five experimental testing visits. Study documents included an informed consent, a detailed health history questionnaire, a health status questionnaire, and HIPAA documents. Upon completion of all paperwork electromyography (EMG) electrode placement for the soleus muscle (of both legs) was measured, as well as the most optimal placement for tibial nerve stimulation, and familiarization to balance testing was performed. Visits two through five consisted of soleus H – reflex testing to determine H_{max} / M_{max}. Each muscle was tested twice in random order, but only once per visit. Visit six consisted of a body composition assessment using dual-energy x-ray absorptiometry (DXA) technology and completion of two different balance tasks programmed on the NeuroCom® Smart Master Balance® system. The Institutional Review Board at the University of Oklahoma approved the study, and all procedures described herein complied with the Declaration of Helsinki.

Control Variables

Testing of each subject was performed at approximately the same time of day throughout the course of the study. Participants were asked to abstain from caffeine, exercise, and alcohol for 12 hours prior to each testing visit and be 2-3 hours post-prandial prior to testing. Hydration status was determined prior to performing the DXA scans (55) scan using a refractometer (VEE GEE Refractometer CLX-1, Kirkland, WA). A value in the range of 1.004-1.029 USG was considered acceptable to conduct the DXA scans. If an individual could not reach acceptable hydration values within 30 minutes of the initial hydration test, the scans were rescheduled for a subsequent visit. All female participants also took a pregnancy test prior to the DXA scans. Based on evidence from Kraus et al., (2009) hydration status was not measured prior to H – reflex testing (25).

All participants were also given a Rochester Fatigue Diary (RFD; a visual analogue scale) to be completed each day enrolled in study, even on days when no testing was conducted to monitor levels of fatigue between visits. The RFD is a measure of lassitude (i.e., lack of energy) that the participants report each hour of the day. If a participant exhibited higher levels of fatigue than normal during the days between testing, he/she was rescheduled for a later date in an attempt to reduce any unwarranted variability in the data.

The Modified Fatigue Severity Scale (MFIS) was used to monitor fatigue on the day of testing. The MFIS is a 21-item questionnaire, measuring physical, social, and cognitive symptomatic fatigue, which uses a summated rating Likert scale to access the impact of fatigue on everyday life (41). Our primary outcome of concern was the *physical* subscale on the MFIS; however, all were reviewed prior to testing. If an

individuals' score deviates more than 2.5 standard deviations from their mean they were rescheduled for testing on a subsequent day.

Visit 1: Screening, Necessary Paperwork, and Familiarization.

Prior to enrollment into the study all subjects were required to obtain documented physician's clearance. Upon initial arrival to the Human Performance Laboratory at the University of Oklahoma all volunteers were screened to confirm they met all inclusion criteria and did not meet any exclusion criteria. Those who met all criteria were provided time to review all study related documents; all questions were answered to the best of the experimenter's ability, and all concerns were addressed accordingly. Once all documents were signed subjects were familiarization to all experimental procedures.

Familiarization to H – reflex Procedures

The purpose of familiarization to H – reflex procedures was to allow participants to become accustomed to the sensations of electrical nerve stimulation. Initially, participants were asked to lie supine on an examination table and EMG electrode sites were determined. Each site was shaved, lightly abraded, and cleansed with isopropyl alcohol prior to the placement of two bipolar EMG electrodes over the soleus muscle and one over the patella. Following EMG electrode placement stimulation electrodes were placed on the leg. The first electrode was placed proximal to the patella (just above the kneecap). Next, low intensity stimulation was applied multiple times (5 – 25) via a handheld electrode to the back of the knee to locate the tibial nerve. Once the nerve was located (confirmed with a visible muscle twitch, plantar flexion movement of the foot, and a reflex response without a M wave in the EMG tracing) a small circular

electrode was affixed in that exact location and subsequently outlined for reliable retest purposes. Following electrode placement, participants were moved to the isokinetic dynamometer (KIN-COM, Isokinetic International, Chattanooga, TN) to finish the familiarization. Participants were positioned in a supine position and their ankle was securely attached to a metal bracket attached to the dynamometer so the angle of the ankle was100 degrees of dorsiflexion and aligned with the axis of the torque motor, and their knee was fully extended. The non-testing limb was also fully extended and supported with a stand of equal height to the testing chair. The thigh of the testing leg was strapped down to prevent hip flexion during stimulation and isolate the stimulation response to stimulation to the ankle joint as much as possible. Participants then received a single 1-millisecond electrical pulse at a low intensity while plantar flexor torque and the raw EMG signal was recorded. Stimulation intensity increased by 0.25 volts every 7 – 10 seconds until the direct motor wave (i.e., M – wave) from the EMG signal plateaued. The H – reflex and M – wave amplitudes from the EMG signal were recorded at each stimulation intensity to construct H – M recruitment curves. Familiarization was performed on both limbs during the first visit.

Familiarization to Balance Testing Procedures

Familiarization to both balance assessments was provided to finish visit 1. Participants were asked to remove their shoes before being fitted with a safety harness (similar to a parachute harness) that catches the participant if he/she were to lose their balance. Once the harness is securely fastened around their chest and waist they were asked to step up onto the specialized force platform (NeuroCom® Smart Balance Master®, Natus Medical Inc., Pleasanton, CA) and align their lateral malleolus with the

dual force plate's axis of rotation. Participants were asked to look forward at a screen approximately one meter away for the duration of each test unless the condition required eyes to be closed. Participants completed a minimum of one trial for each condition of the two balance tests, which included a Sensory Organization Test (SOT) and a Limits of Stability (LOS) protocol. If a participant did not feel comfortable with a test or condition they were provided additional trials until they were comfortable with the test.

General Questionnaires

Health History and Health Status Questionnaire

The health history and health status questionnaire requested the necessary information about all past health complications that indicated the participant might be at an increased risk by participating in physical activity. This form also required any medications the participant was taking to be listed, as well as a summary of the frequency and types of exercise each participant has performed over the previous six months.

Anthropometrics

Standing Height

Height was measured to the nearest 0.5 cm using a stadiometer (Seca Model 242, Chino, CA). The participants were asked to remove their shoes and place their heels together, take a deep breath, and stand up tall with their head aligned in the sagittal plane.

Body Mass and Body Mass Index

Body mass was measured to the nearest 0.1 km using a digital electronic scale (Tanita Model WB-627A, Tokyo, Japan) with participants wearing light clothing and no shoes. The body mass index (BMI) was calculated as the body mass in kilograms divided by the standing height in meters squared (kg/m^2).

Body Composition

Total body and lower-leg composition was quantified using a DXA scanner (GE Healthcare, Schenectady, NY). The purpose of this test was to compare total body composition and composition of the lower-legs between participants. Defining custom regions of interest for each leg quantified lower-leg body composition and allowed for comparison. Specifically, the ROI for analysis was created by drawing a rectangular box over the lower-leg with the upper boundary bisecting the center of the knee joint and the lower boundary bisecting the ankle joint just distal to the lateral malleolus. ROIs were quality checked by two testers. If a female participant was premenopausal, a pregnancy test was conducted before performing the body scans.

MS Specific Questionnaires

In addition to the initial screening and familiarization procedures, all participants were asked to complete two fatigue questionnaires, a modified fatigue impact scale (MFIS) at the beginning of each test visit and a Rochester Fatigue Diary (RFD) everyday enrolled in study.

Modified Fatigue Impact Scale (MFIS)

The MFIS is a 21-item questionnaire that measures physical, social, and cognitive symptomatic fatigue, and uses a Likert scale to access the impact of fatigue on

everyday life. This questionnaire has the subjects describe their own fatigue by answering a variety of questions on a scale of 0-4; a 0 indicates having never experienced this fatigue symptom and 4 indicates almost always experiencing this fatigue symptom. The questionnaire is scored on a subscale of physical, cognitive, and psychosocial fatigue based on specific questions, as well as a total score. This questionnaire was administered on every testing visit and if the physical subscale of the MFIS is 2.5 standard deviations greater than the running mean the subjects were asked to reschedule the testing visit to a later date when fatigue levels returned to normal.

Rochester Fatigue Diary (RFD)

The RFD is a measure of lassitude in MS patients. The RFD consists of 24 vertical bars for each subject to rate the severity of fatigue on a visual analog scale at each hour of the day (60). The location of the hourly mark is converted to 0 (maximal fatigue) to 100 (no fatigue) and then averaged for a daily fatigue score; sleep is given a score of zero. The advantage of RFD is that it allows the subject to assess their own lassitude and is less subjective to recall bias of other fatigue questionnaires (60). The RFD was given to all participants to take home to be completed every day during the duration of the study and was measured at the beginning of each test visit. The variability of fatigue was monitored similar to the MFIS in that any significant deviation between scores longer than 48 hours along with changes in MFIS resulted in the participant to reschedule the testing visit to a later date when the fatigue levels have normalized as done previously (29, 30).

Visits 2 – 5: H – reflex Testing

On visits 2 through 5 the soleus H – reflex testing occurred. H – M recruitment curves were constructed by progressively increasing the electrical stimulus in 0.25-volt increments to find the greatest peak-to-peak amplitude of the H – reflex (H_{max}) and M – wave (M_{max}). Three to five trials were performed and averaged at each intensity to determine H_{max} and M_{max}. A minimum of 24 hours but no more than 120 hours (i.e., five days) separated visits two through five.

Surface Electromyography (EMG)

Pre-gelled bipolar surface EMG (BIOPAC® Systems, Inc., Goletta, CA) signals were collected from the soleus muscle during H – reflex testing. Following careful preparation of skin, which included shaving, gently abrading, and cleansing with alcohol, surface EMG electrodes (EL503, circular, Ag/AgCl, 10mm diameter, BIOPAC® Systems, Goletta, CA) with an inter-electrode distance of 2 cm were placed on soleus muscle in accordance with SENIAM recommendations. Specifically, placement was 2/3 of the line originating from the medial condylis of the femur and extending down through the medial malleolus at the talocrural (i.e., ankle) joint. Reliability in EMG measurements were controlled by carefully marking surface electrode placement with a permanent marker prior to electrode removal. Participants were encouraged to retrace the original placement outline between visits.

EMG Signal Acquisition

The soleus muscle EMG signal was sampled at a frequency of 1000Hz, amplified with a gain of 500Hz, and filtered with a band-pass filter using a low cutoff frequency of 10 Hz and a high cutoff frequency of 500 Hz.

Soleus H – reflex

The H reflex was elicited by applying a percutaneous electrical current superficial to the tibial nerve in the popliteal fossa located on the posterior aspect of the patellofemoral (i.e., knee) joint while in a fully- reclined, supine position with head fixed in a stable position, the testing ankle flexed 100°, and the testing foot securely strapped to a metal platform attached to a load cell (Kin Com, Chattanooga, TN). Stimulation electrodes used consisted of a 1.25" anode and a 2.0" cathode just proximal to the patella. The most optimal stimulating site was located using a handheld stimulating pen. Once the most optimal site for stimulation is located a 1.25" self-adhesive cathode was placed at that site and a 2" anode was placed just proximal to the patella. Stimulus duration was 1-ms [rectangular] pulses delivered by a manufactured stimulator (STMISOLA and STM100C BIOPAC Systems, Inc., Goletta, CA). An inter-stimulus duration of ten seconds was provided to reduce post-activation depression. Twitch torque of the ankle plantar flexors was collected during stimulation and filtered using a low-pass filter set to 4Hz.

H – Reflex / M – Wave Recruitment Curve

An H – reflex recruitment curve was constructed by plotting the peak-to-peak amplitude recorded from the surface EMG electrodes placed over the soleus muscle. The H reflex eventually reaches a peak referred to as the H_{max}, and a second response begins to appear in the EMG recording, referred to as the M wave. As stimulation intensity continues to progressively increase the H reflex will decrease, eventually becoming completely absent from the EMG recording, and the M wave will reach a plateau (M_{max}).

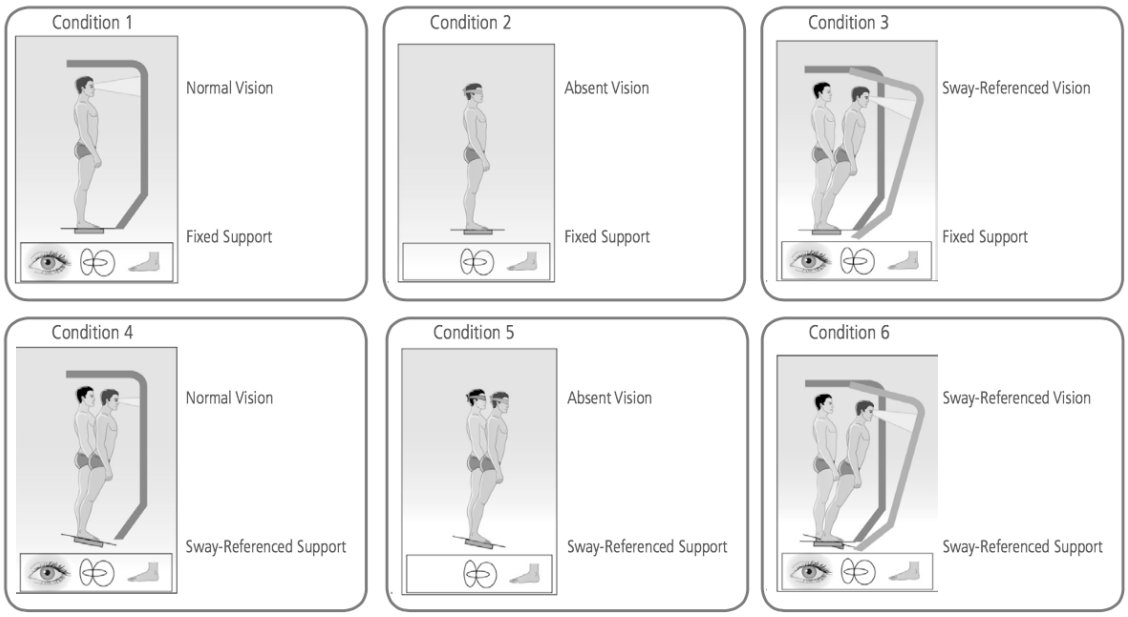
Visit 6: DXA & Balance Testing

On visit 6 subjects initially provided a urine sample to determine hydration and pregnancy (if female) status before having a dual energy x-ray absorptiometry (DXA) body scan to determine bone density, fat-mass, and fat-free mass. Following the DXA scan two balance assessments were completed separated by 10 minutes on a specialized force platform (NeuroCom® Smart Balance Master® System, Natus Medical Inc., Pleasanton, CA). Subjects were fitted with a parachute harness and attached to a steel crossbar on the top of the testing unit with heavy-duty metal clips to prevent falling during testing. After all required information was entered into the system subjects were instructed to step up onto the testing platform (i.e., a rocking dual force plate) and align their body such that their lateral malleolus lines up with the axis of rotation of the platform. To confirm correct body position on the testing platform the subject's COG was displayed on a screen and was as close to the center of the crosshairs in the COG plot.

The Sensory Organization Test (SOT) was used to assess impairments in postural control, effective use of sensory systems (i.e., vestibular, visual, somatosensory), and visual-vestibular conflict resolution. The SOT consists of six different conditions that were performed a total of three times (Figure 1). During the SOT, inaccurate information delivered to the participant's eyes, feet, and/or joints is controlled through a calibrated sway referencing of the support surface and/or visual surround resulting in sensory conflict. The *equilibrium* score quantifies the center of gravity sway or postural stability during each of the three trials of the six conditions. The *composite equilibrium* score characterizes the participant's overall level of performance. Sensory analysis ratios were developed to identify impairments in

individual sensory systems. Accurate integration of sensory information is critical to maintaining balance within a variety of environments encountered in daily life. An inability to appropriately integrate and organize sensory information can lead to impairments in COG alignment and/or selection of movement strategies.

Figure 1. Sensory Organization Test Conditions.



The Limits of Stability (LOS) test quantifies impairments in a participant's ability to intentionally displace their COG to their theoretical stability limit (i.e., 12.5 °) without losing balance. A real time display of their COG relative to the directional target was provided. A total of eight directions were tested. On command, the participant displaced their COG as quickly and accurately as possible towards a target located on the LOS perimeter, and held that position as close to the target as possible. Each direction was eight seconds in duration.

LOS analysis includes reaction time, movement velocity, endpoint excursion, maximum excursion, and directional control. The ability to voluntarily change the COG

to positions within the LOS is fundamental to mobility tasks such as reaching tasks, transitioning from sitting to standing (or vice-versa), and walking.

Data Management and Analysis

All required documents will be stored in a locked filing cabinet in the Human Performance Lab at the University of Oklahoma, and acquired data will be stored on a password protected Excel® spreadsheet on a password protected personal computer in the Human Performance Lab at the University of Oklahoma. All data was de-identified and saved using a specific code for each participant.

Statistics

Data was smoothed by averaging the peak-to-peak amplitude of the H – reflex and M – wave recordings at each intensity (51). The data was then analyzed to determine the stimulation intensity that evoked the maximum amplitude in the H – reflex and M – wave in order to calculate the H_{max} / M_{max} ratio. Asymmetry scores were calculated for H_{max} / M_{max} by averaging the H_{max} / M_{max} ratios from both days, and then turning the average of both limbs into a percentage calculated as: $1 - [\frac{smaller\ H/M}{larger\ H/M}] \times 100$ (5). Asymmetry scores were compared between groups with independent t-tests.

All analyses will be performed using SigmaPlot Software 12.5 (Systat Software, San Jose, CA). Paired t-tests were used to identify within-limb differences across the four visits (i.e., left leg 1vs. left leg 2 and right leg 1 vs. right leg 2). The H_{max} / M_{max} ratios of each leg were averaged and compared using independent t-tests. Data was reported as mean ± SD, unless otherwise noted. Pearson correlations were run between soleus H_{max} / M_{max} asymmetry scores and all SOT conditions as well as SOT composite equilibrium scores, and the four cardinal directions associated with the LOS test.

Correlations were run with the groups pooled and separate. Cohen's d effect sizes (ES) were calculated for all comparisons with ≤ 0.20 indicating a small effect, 0.50 indicating a moderate effect, and ≥ 0.80 indicating a large effect.

Absolute and relative reliability was determined for H reflex measures. Absolute reliability was reported as standard error of the measurement (SEM). SEM was calculated as $\sqrt{MSerror}$. Relative reliability was reported as $ICC_{3,1}$. Level of significance was set a priori at $p \leq 0.05$.

Table 1. Overview of study

	Protocol	**Time Commitment**
Visit 1	1. Paperwork 2. Determine location of EMG and stimulation electrodes 3. Familiarization to balance tests.	2 hours
Visits 2 – 5	1. Acquisition of soleus H – reflex and M – waves from left and right legs. Visits will be randomized.	8 hours
Visit 6	1. DXA body scan 2. Sensory Organization Test 3. Limits of Stability	2 hours
Total		12.0 hours

CHAPTER IV: RESULTS & DISCUSSION

Results

Participant Characteristics

Seventeen participants (MS: 9 and Control: 8) were consented, but one person with MS withdrew from the study after the first visit leaving eight participants in the MS group. Five of the MS participants were females (age = 48.9 ± 13.9 years, height = 171.5 ± 6.1 cm, weight = 92.7 ± 25.1 kg, EDSS = 3.1 ± 2.2) and three were males (age = 51.2 ± 7.7 years, height = 176.7 ± 4.2 cm, weight = 97.5 ± 16.6 kg, EDSS = 3.2 ± 2.0). Six of the non-MS participants were females (age = 43.5 years, height = 163.8 ± 4.5 cm, weight = 77.5 ± 26.4 kg) and two were males (age = 64.0 ± 0.0 years, height = 180.0 ± 4.2 cm, weight = 99.6 ± 3.6 kg). The age range for the MS group was 31 to 64, and the age range for the Non-MS group was 31 to 64. The diagnoses of the MS participants were as follows: two primary progressive, and six relapsing-remitting. The mean ± SD EDSS score for the MS group was 3.3 ± 2.2 (range = 1 to 6; median = 2) indicating a mild to moderate degree of disability in the MS sample. No visits had to be rescheduled due to levels of fatigue. Descriptive characteristics for both groups are summarized in Table 2. The groups were similar in age, height, body mass, lean mass, BMI, and physical activity (self-reported). The MS group had significantly greater total body fat mass (Non-MS: 24.9 ± 8.2 kg. vs. MS: 42.1 ± 15.8 kg, $p = 0.02$) and body fat % (Non-MS: 34.1 ± 7.7 % vs. MS: 45.1 ± 7.7 %, $p = 0.01$). Lower-leg lean mass, fat-mass, and fat mass % did not differ significantly between groups and are summarized in Table 3.

Table 2. Participant descriptive characteristics (mean ± SD; *n* = 8 per group).

	Non-MS	MS	95% CI	*P*
Age (yr.)	48.6 ± 11.3	49.9 ± 11.1	-10.7 to 13.2	0.83
Height (cm.)	167.9 ± 8.5	173.3 ± 5.7	-2.2 to 13.4	0.14
Body Mass (kg.)	83.0 ± 24.6	94.5 ± 21.1	-13.0 to 36.2	0.33
Lean Mass (kg.)	47.2 ± 10.9	49.1 ± 7.5	-8.1 to 11.9	0.69
Fat Mass (kg.)	24.9 ± 8.2	42.1 ± 15.8	3.7 to 30.7	**0.02**
Fat Mass (%)	34.1 ± 7.7	45.1 ± 7.7	2.7 to 19.2	**0.01**
BMI (kg * m^{-2})	29.3 ± 8.5	28.9 ± 6.8	-6.2 to 10.3	0.60
PA (min * $week^{-1}$)	120.0 ± 81.8	206.3 ± 89.6	-178.2 to 5.7	0.06
EDSS	NA	3.1 ± 2.2	1.8	NA

MS, multiple sclerosis; BMI, body mass index; PA, self-reported physical activity; EDSS, expanded disability status score; 95% CI, 95% confidence interval for the difference of group means.

Table 3. Lower-leg composition (mean ± SD; *n* = 8 per group).

	Group	Left	Right	95% CI	*P*	ES
Lean Mass	Non-MS	2.02 ± 0.5	1.98 ± 0.4	-0.03 to 0.12	0.23	0.08
(kg)	MS	1.99 ± 0.3	2.05 ± 0.3	-0.11 to 0.004	0.06	-0.17
Fat Mass	Non-MS	1.01 ± 0.4	1.08 ± 0.7	-0.81 to 0.66	0.82	-0.13
(kg)	MS	1.30 ± 0.6	1.35 ± 0.7	-0.15 to 0.06	0.36	-0.07
Fat Mass	Non-MS	28.8 ± 6.0	29.6 ± 7.3	-2.48 to 0.98	0.34	-0.13
(%)	MS	38.1 ± 9.5	37.8 ± 10.4	-1.30 to 1.90	0.68	0.03

MS, multiple sclerosis; 95% CI, 95% confidence interval between limbs-within group; ES, effect size.

Test Reliability

All stimulation visits were scheduled near the same time of each day to improve consistency across visits. Pearson correlation coefficients (r), intraclass correlation coefficients (ICC), and standard error of measurement (SEM) were calculated for the soleus H_{max} / M_{max} ratios and are summarized in Table 4. Both groups demonstrated strong within-limb reliability in both limbs. Between limb H_{max} / M_{max} reliability was less consistent in the MS group (r = 0.45, CI = -0.37 to 0.88; ICC = 0.52, CI = -0.22 to 0.88; SEM = 5.87), but remained strong in the control group, and is summarized in Table 5.

Table 4. Within-limb reliability for soleus H / M ratios (n = 8 per group).

Group	Limb / Visit	Pearson	ICC	SEM
Non-MS	Left 1 & 2	0.98 (CI: 0.87 to 1.00)	0.97 (CI: 0.88 to 0.99)	0.07
	Right 1 & 2	0.93 (CI: 0.66 to 0.99)	0.95 (CI: 0.79 to 0.99)	0.07
MS	Left 1 & 2	0.92 (CI: 0.60 to 0.99)	0.94 (CI: 0.74 to 0.99)	0.07
	Right 1 & 2	0.89 (CI: 0.49 to 0.98)	0.91 (CI: 0.62 to 0.98)	0.06

MS, multiple sclerosis; CI, 95% confidence limits; ICC, intraclass correlation; SEM, standard error of the measurement.

Table 5. Between-limb reliability for soleus H / M ratios (n = 8 per group).

Group	Pearson	ICC	SEM
Non-MS	0.96 (CI: 0.78 to 0.99)	0.97 (CI: 0.88 to 0.99)	1.39
MS	0.45 (CI: -0.37 to 0.88)	0.52 (CI: -0.22 to 0.88)	5.87

MS, multiple sclerosis; CI, 95% confidence limit; ICC, intraclass correlation; SEM, standard error of measurement.

Maximum H / M

Between-limb and within-limb average H_{max} / M_{max} values for both groups are summarized in Tables 6 and 7 respectively. Between limb H_{max} / M_{max} values were similar within each group (Non-MS: Left = 0.603 ± 0.198 vs. Right = 0.601 ± 0.197, p = 0.905, ES = 0.01; Figure 1; MS: Left = 0.743 ± 0.172 vs. Right = 0.643 ± 0.197, p = 0.188, ES = 0.58; Figure 2). A significant H_{max} / M_{max} difference was observed between test visits within the same limb in the control group for the right leg (Right leg 1 = 0.643 ± 0.197 vs. Right leg 2 = 0.558 ± 0.203mV, p = 0.02, ES = 0.45; Figure 3), but not the left (Left leg 1 = 0.596 ± 0.215 vs. Left leg 2 = 0.610 ± 0.184mV, p = 0.564, ES = -0.07). The MS group's within-limb – between visits H_{max} / M_{max} were similar for both legs (Left leg 1 = 0.754 ± 0.187mV vs. Left leg 2 = 0.732 ± 0.165mV, p = 0.413, ES = 0.13; Right leg 1 = 0.667 ± 0.225mV vs. Right leg 2 = 0.619 ± 0.180mV, p =

0.236, ES = 0.25; Figure 4). The MS group had a significantly greater H_{max} / M_{max} asymmetry score (Non-MS = 4.6 ± 3.9% vs. MS: 21.7 ± 16.6%, p = 0.01, ES = 1.51; Figure 5). H_{max} / M_{max} asymmetry scores are summarized in Table 8 and displayed in Figure 6. Percent difference between legs in H_{max} / M_{max} ratios are displayed in Figure 7. Individual MS and Non-MS averaged H_{max} / M_{max} ratios for each leg are presented in Figures 8 and 9 respectively.

Table 6. Soleus H_{max} / M_{max} scores between legs (mean ± SD; *n* = 8 per group).

	Group	Left	Right	95% CI	*P*	ES
H / M (%)	Non-MS	0.603 ± 0.198	0.601 ± 0.197	-0.05 to 0.05	0.91	0.01
	MS	0.743 ± 0.172	0.643 ± 0.197	-0.06 to 0.26	0.19	0.58

MS, multiple sclerosis; H / M, maximum Hoffmann reflex /maximum M wave; 95% CI, 95% confidence interval for difference between limbs; ES, effect size.

Table 7. Within-leg H_{max} / M_{max} (n = 8 per group).

		Visit 1	Visit 2	95% CI	*P*	ES
Non-MS	Left	0.596 ± 0.215	0.610 ± 0.184	-0.06 to 0.04	0.56	-0.07
	Right	0.643 ± 0.197	0.558 ± 0.203	0.02 to 0.15	**0.02**	0.45
MS	Left	0.754 ± 0.187	0.732 ± 0.165	-0.04 to 0.09	0.41	0.13
	Right	0.667 ± 0.225	0.619 ± 0.180	-0.04 to 0.13	0.24	0.25

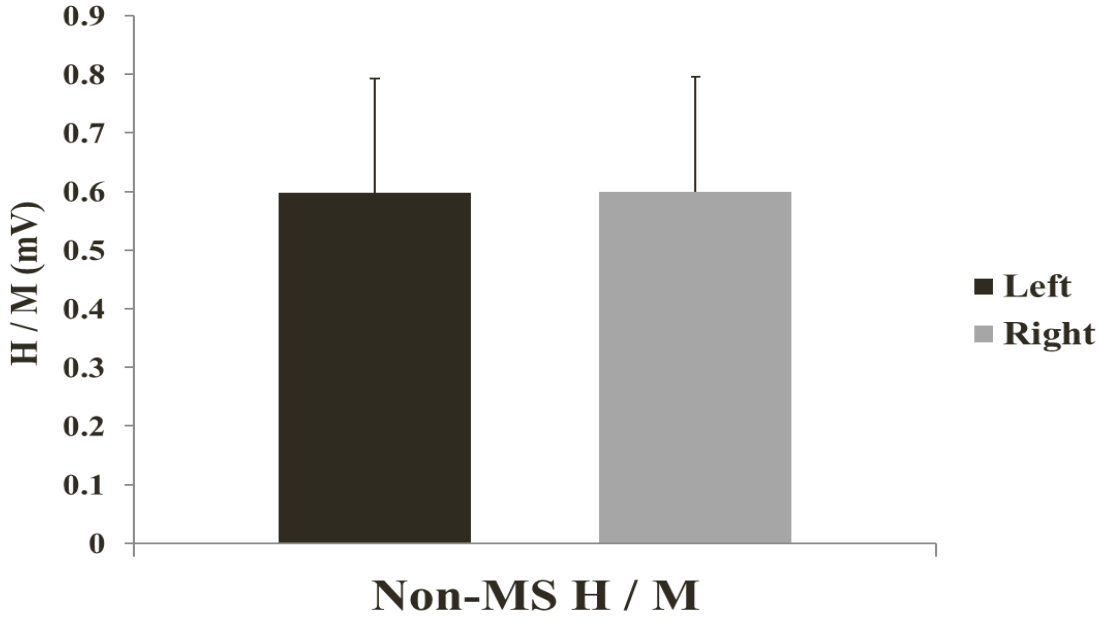
MS, multiple sclerosis; ES, effect size.

Table 8. Soleus H_{max} / M_{max} bilateral asymmetry score (mean ± SD; *n* = 8 per group).

	Non-MS	MS	95% CI	*P*	ES
H / M Asymmetry (%)	4.6 ± 3.9	21.7 ± 16.6	-30.0 to -4.1	**0.01**	1.51

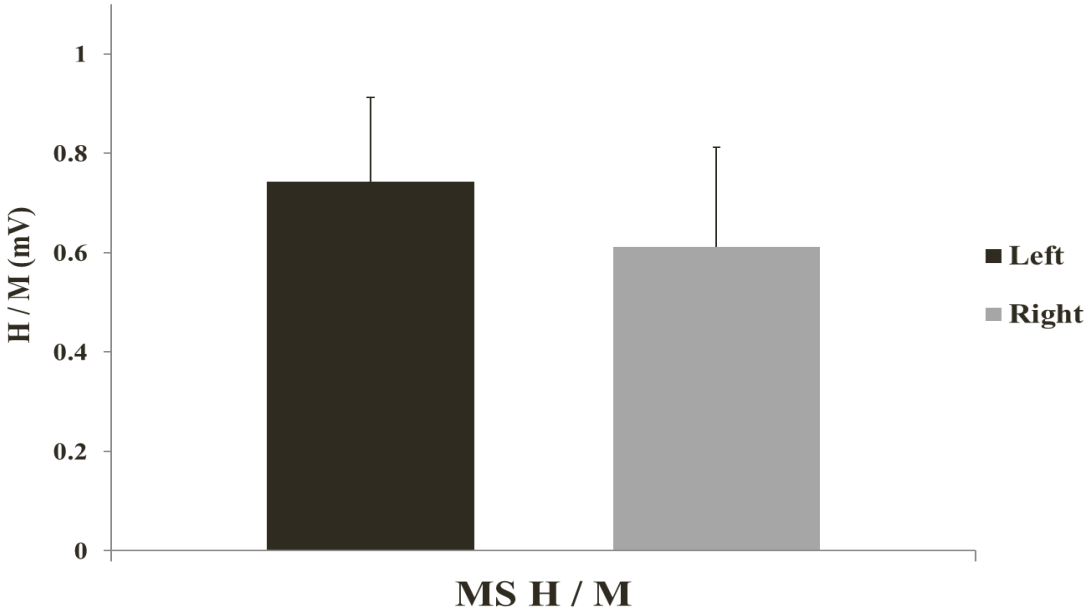
MS, multiple sclerosis; H / M, maximum Hoffmann reflex /maximum M wave; 95% CI, 95% confidence interval for difference between limbs; ES, effect size.

Figure 2. Between-Limb Soleus H_{max} / M_{max} for Left and Right Leg in Non-MS Participants.



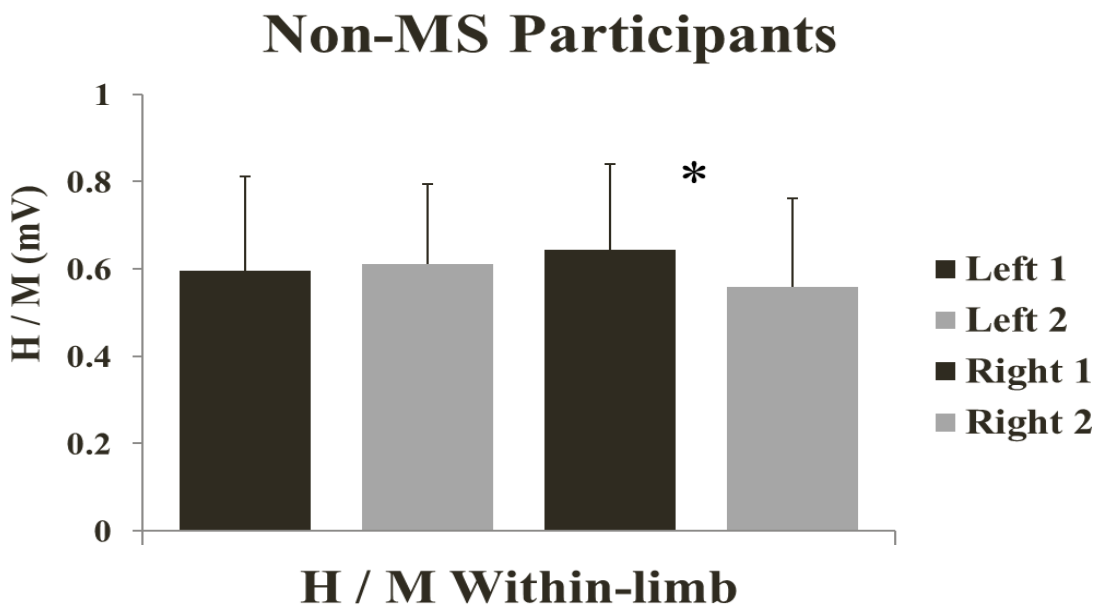
Data are presented as mean ± SD.

Figure 3. Between-Limb Soleus H_{max} / Mmax for Left and Right Leg in MS Participants.



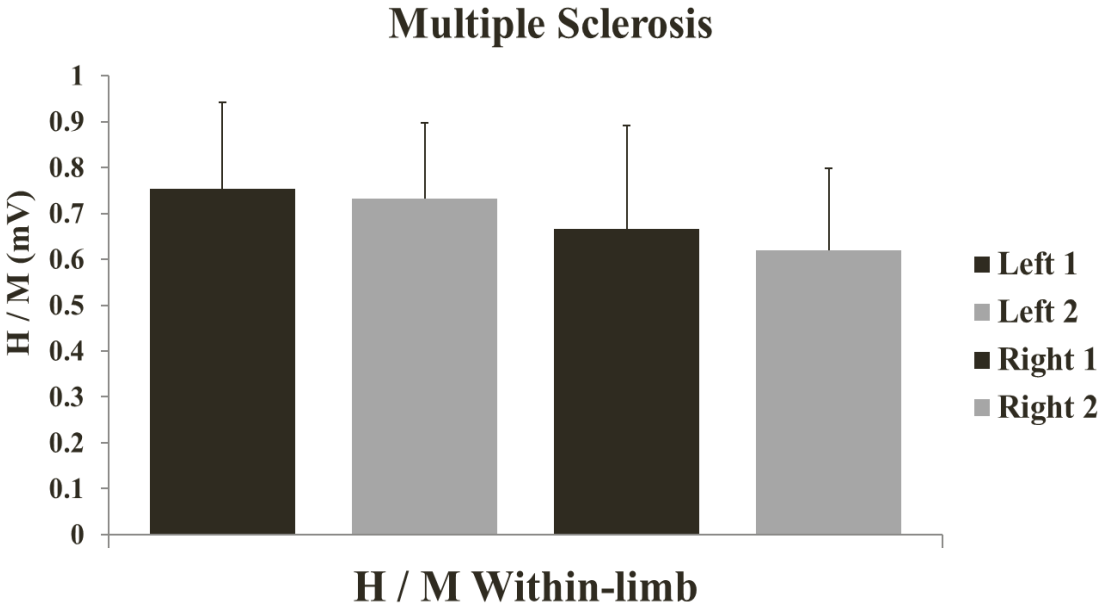
Data are presented as mean ± SD.

Figure 4. Within-Limb Soleus H_{max} / M_{max} for Left and Right Leg in Non-MS Participants.



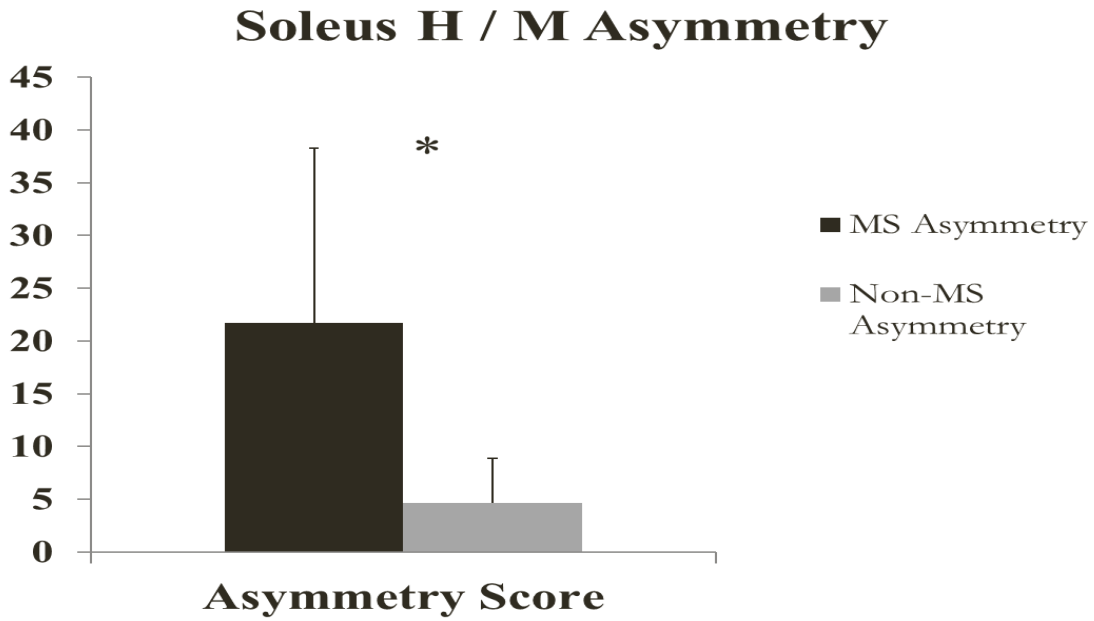
Data are mean ± SD. * denotes p < 0.05.

Figure 5. Within-Limb Soleus H_{max} / M_{max} for Left and Right Leg in MS Participants.



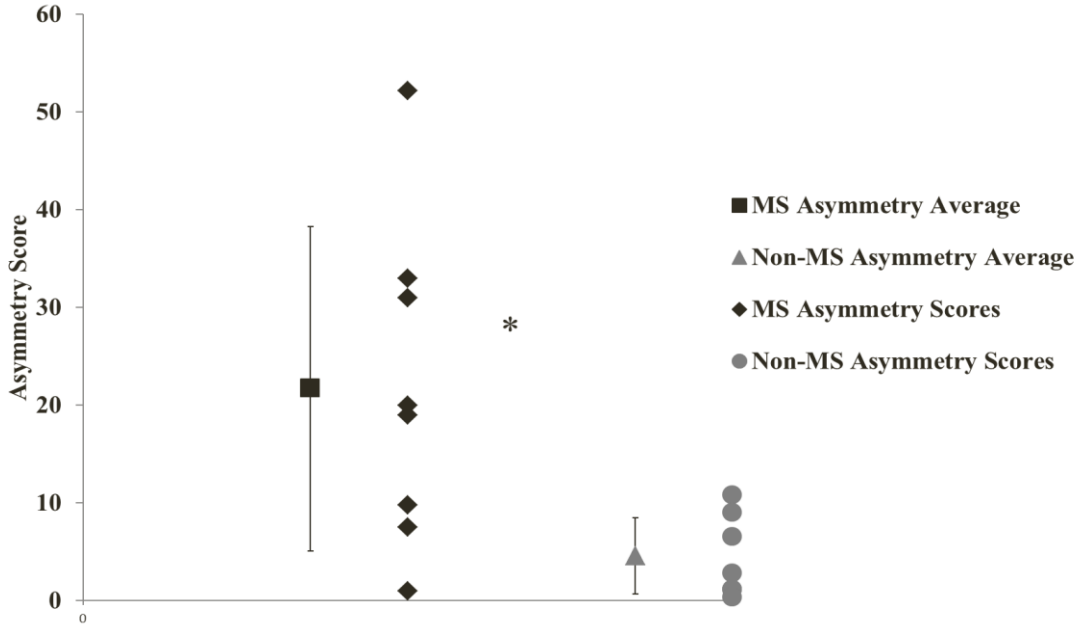
Data are presented as mean ± SD.

Figure 6. Soleus H_{max} / M_{max} Asymmetry Scores for MS and Non-MS Participants.



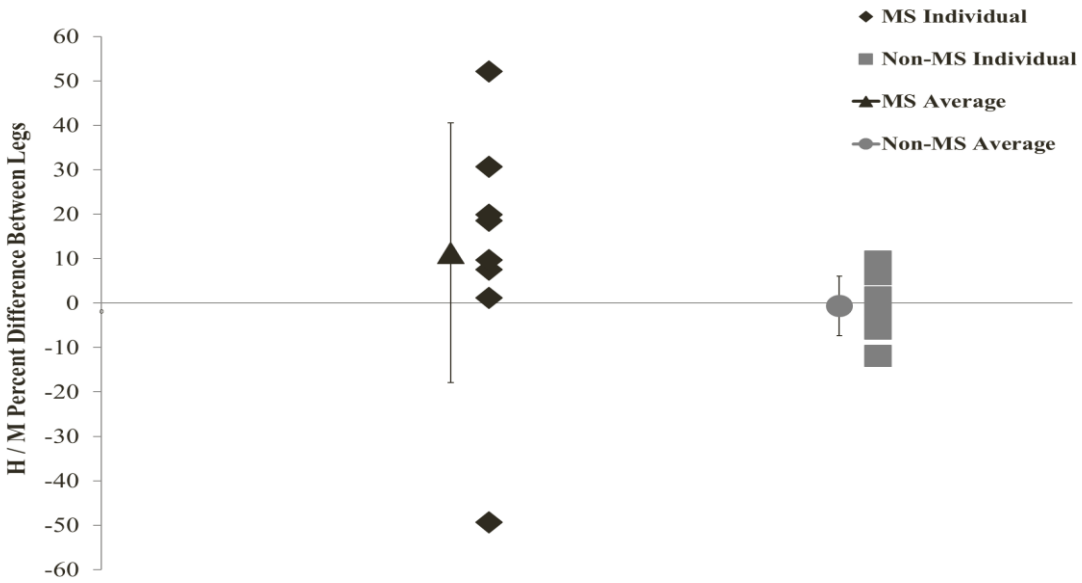
Data are presented as mean ± SD. * denotes p ≤ 0.01.

Figure 7. Individual and Average H_{max} / M_{max} Asymmetry Scores for Both MS and Non-MS Participants.



Vertical whiskers represent SD of the average values. * denotes p < 0.01 for average asymmetry scores between groups.

Figure 8. Individual and Average Percent Difference for H_{max} / M_{max} Between Legs for Both MS and Non-MS Participants.



Vertical whiskers represent SD of the average values.

Sensory organization test

All results for SOT conditions are summarized in Table 9 and displayed in Figure 10. The MS group performed significantly worse during the SOT 1 condition (Non-MS: 96.0 ± 1.5 vs. MS: 93.1 ± 3.1, p = 0.04, ES = -1.25). No significant difference between groups was observed for SOT 2 (eyes closed with fixed reference and support). The MS group performed significantly worse during SOT conditions three through six (Condition 3: Non-MS: 92.6 ± 3.9 vs. MS: 86.7 ± 4.9, p = 0.02, ES = -1.43; Condition 4: Non-MS: 91.1 ± 2.0 vs. MS: 85.5 ± 4.0, p = 0.002, ES = -1.89; Condition 5: Non-MS: 76.3 ± 5.7 vs. MS: 69.6 ± 5.0, p = 0.02, ES = -1.35; Condition 6: Non-MS: 80.6 ± 5.1 vs. 72.0 ± 7.0, p = 0.01, ES = -1.50). The composite equilibrium score from

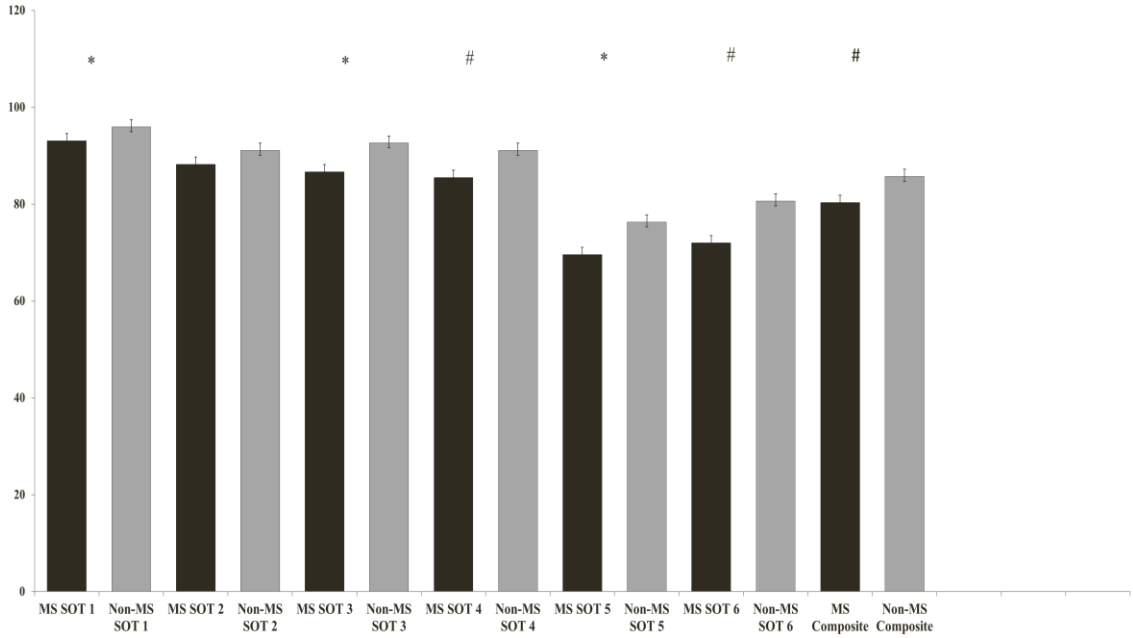
the SOT indicated the MS group performed significantly worse than the Non-MS group (Non-MS: 85.8 ± 2.9 vs. MS: 80.4 ± 4.0, p = 0.01, ES = -1.65).

Table 9. Sensory Organization Test (mean ± SD; *n* = 8 per group).

	Non-MS	MS	95% CI	*P*	ES
SOT Composite	85.8 ± 2.9	80.4 ± 4.0	-9.1 to -1.70	**0.01**	- 1.65
SOT 1	96.0 ± 1.5	93.1 ± 3.1	-5.4 to -0.24	**0.04**	- 1.25
SOT 2	91.1 ± 4.3	88.2 ± 4.5	-7.6 to 1.80	0.21	- 0.71
SOT 3	92.6 ± 3.9	86.7 ± 4.9	-10.7 to -1.20	**0.02**	- 1.43
SOT 4	91.1 ± 2.0	85.5 ± 4.0	-9.0 to -2.20	**0.002**	- 1.89
SOT 5	76.3 ± 5.7	69.6 ± 5.0	-12.5 to -1.00	**0.02**	- 1.35
SOT 6	80.6 ± 5.1	72.0 ± 7.0	-15.2 to -2.00	**0.01**	- 1.50

SOT, sensory organization test; MS, multiple sclerosis; 95% CI, 95% confidence interval of group means; ES, effect size

Figure 9. Sensory Organization Test Results for Both MS and Non-MS Participants.



Data are presented as mean ± SD. * denotes p < 0.05, # denotes p ≤ 0.01.

Limits of stability (Forward Direction)

All results for the forward direction LOS test are summarized in Table 10 and displayed in Figure 11. Reaction time was similar between groups, but had a moderate

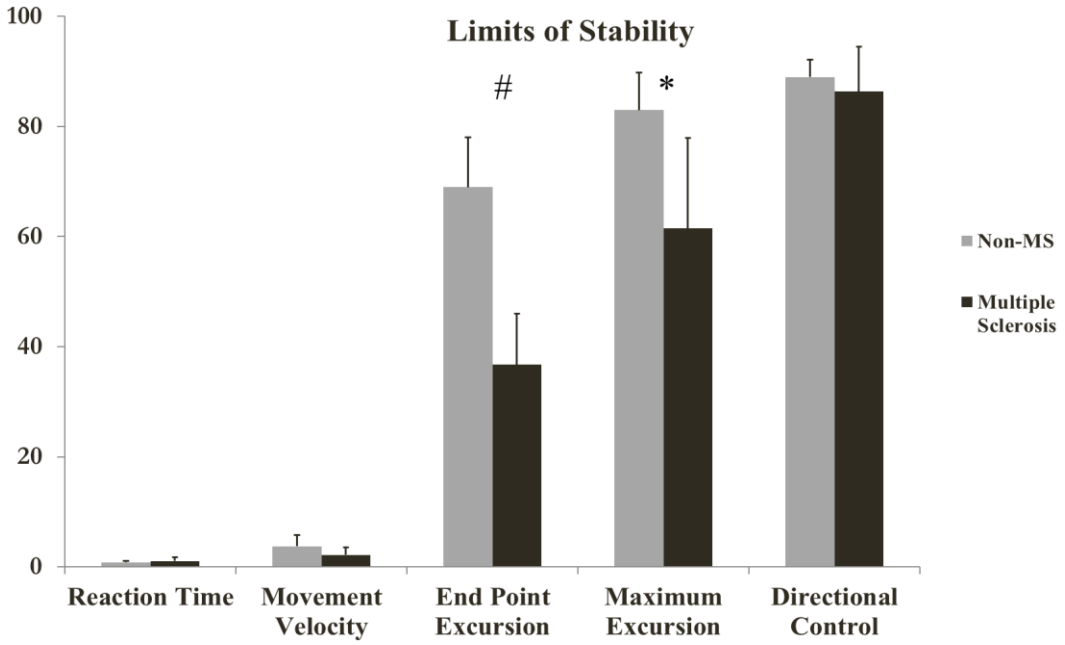
effect (Non-MS: 0.83 ± 0.29 seconds vs. MS: 1.05 ± 0.74 seconds, p = 0.45, ES = 0.41). Movement velocity was similar between groups, but had a moderate effect (Non-MS: 3.71 ± 2.18 degrees * second^{-1} vs. 2.16 ± 1.33 degrees * second^{-1}, p = 0.108, ES = -0.60). A significant difference and very strong effect was observed between groups for end point excursion with the MS group performing worse than the Non-MS group (Non-MS: 69.0 ± 11.4% vs. MS: 36.8 ± 9.2%, p = 0.00002, ES = -3.33). A significant difference and strong effect was observed between groups for maximum excursion with the MS group performing significantly worse than the Non-MS group (Non-MS: 83.0 ± 10.2% vs. MS: 61.5 ± 16.4, p = 0.007, ES = -1.68). Directional control was similar between groups, but had a moderate effect (Non-MS: 89.0 ± 4.8% vs. 86.4 ± 8.2%, p = 0.45, ES = -0.42).

Table 10. Forward direction limits of stability (mean ± SD; *n* = 8 per group).

	Non-MS	MS	95% CI	*P*	ES
Reaction Time (s)	0.83 ± 0.29	1.05 ± 0.74	-0.4 to 0.82	0.45	0.41
Movement Velocity (° * s^{-1})	3.71 ± 2.18	2.16 ± 1.33	-3.5 to 0.39	0.11	- 0.60
End Point Excursion (%)	69.0 ± 11.40	36.8 ± 9.20	-43.4 to -21.1	**0.00002**	- 3.33
Maximum Excursion (%)	83.0 ± 10.20	61.5 ± 16.4	-36.1 to -6.90	**0.007**	- 1.68
Directional Control (%)	89.0 ± 4.80	86.4 ± 8.20	-9.8 to 4.60	0.45	- 0.42

MS, multiple sclerosis; 95% CI, 95% confidence interval of group means; ES, effect size.

Figure 10. Limits of Stability Test Results for Both MS and Non-MS Participants.



Data are presented means ± SD. * denotes p < 0.01, # denotes p < 0.0001.

Relationship Between H_{max} / M_{max} Asymmetry and Balance

SOT composite, SOT 1, SOT 2, SOT 3, SOT 5, and SOT 6 were not correlated to H_{max} / M_{max} asymmetry ($p > 0.05$). SOT 4 was negatively correlated to H / M asymmetry ($r = - 0.577$, $p = 0.02$), such that those with greater asymmetry performed worse (Table 11).

LOS forward direction reaction time, endpoint excursion, maximum excursion, and directional control were all associated with H_{max} / M_{max} asymmetry. Specifically, reaction time was positively correlated with H_{max} / M_{max} asymmetry, while endpoint excursion, maximum excursion, and directional control were all negatively correlated to H_{max} / M_{max} asymmetry. LOS forward direction correlations are summarized in Table 12.

Table 11. Correlation coefficients for relationships between H_{max} / M_{max} asymmetry score and six sensory organization test conditions and composite score (*n* = 16).

	H_{max} / M_{max} Asymmetry Score	
	r	***P***
SOT Composite	- 0.351	0.182
SOT 1	- 0.105	0.669
SOT 2	- 0.199	0.460
SOT 3	- 0.284	0.286
SOT 4	- 0.577	**0.020**
SOT 5	- 0.297	0.263
SOT 6	- 0.343	0.194

SOT, sensory organization test.

Table 12. Correlation coefficients for relationships between H_{max} / M_{max} asymmetry score and limits of stability in the forward direction (*n* = 16).

LOS Forward Direction	**H / M Asymmetry Score**	
	r	*P*
Reaction Time (s)	0.518	**0.04**
Movement Velocity ($° * s^{-1}$)	-0.418	0.107
Endpoint Excursion (%)	-0.625	**0.01**
Maximum Excursion (%)	-0.709	**0.002**
Directional Control (%)	-0.615	**0.01**

LOS, limits of stability.

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. The soleus Hoffmann reflex, reported as H_{max} / M_{max} in the present study, was not statistically difference between limbs in either our groups.
2. When H_{max} / M_{max} was converted to an asymmetry score there was a significantly difference between groups with a greater asymmetry score in our MS patients.
3. Within-limb H_{max} / M_{max} appears to a reliable measure as both groups had large ICCs and Pearson's r.
4. H_{max} / M_{max} asymmetry was significantly correlated with condition four of the SOT assessment when both groups were pooled.
5. H_{max} / M_{max} asymmetry was positively correlated with forward direction LOS reaction time, and negatively correlated with endpoint excursion, maximum excursion, and directional control when both groups were pooled together.

The purpose of this study was two-fold. First we sought to learn whether or not limb to limb differences in the soleus H_{max} / M_{max} ratio existed in a sample of MS patients and non-MS participants; and whether this difference between limbs – reported as an asymmetry score – differed between groups. Secondly, we wanted to determine if

H_{max} / M_{max} asymmetry was correlated with balance performance. We hypothesized that between-limb soleus H_{max} / M_{max} ratios would differ in the MS group but not the non-MS group, and that the between-limb difference would be greater in the MS group when compared to the non-MS group. Next, we hypothesized that the H_{max} / M_{max} asymmetry would be related to balance performance. Results indicated no significant difference between the left and right soleus H_{max} / M_{max} ratios in neither the MS group nor the non-MS group; therefore, this hypothesis was rejected. Our H_{max} / M_{max} asymmetry scores ranged from 1 to 52.2 (median = 19.5) in our MS patients and 0.3 to 10.5 (median = 4.2) in our non-MS participants, which resulted in a significant difference between groups ($p < 0.05$, ES = 1.51), which agreed with our hypothesis.

With respect to balance, the SOT composite equilibrium score was not related to soleus H_{max} / M_{max} asymmetry, but when each individual condition was examined a significant relationship ($r = - 0.577$, $p < 0.05$) was identified between H_{max} / M_{max} asymmetry and condition four (eyes open and a sway referenced support). Additional relationships were identified between H_{max} / M_{max} asymmetry and the LOS test; therefore this hypothesis was not fully rejected. Specifically, we observed significant negative relationships between H_{max} / M_{max} asymmetry and endpoint excursion ($r = -0.625$, $p < 0.01$), maximum excursion ($r = -0.709$, $p < 0.01$), and directional control ($r = -0.615$, $p < 0.05$) – all in the forward direction. These results indicate that as reflex asymmetry increased the initial distance travelled towards the forward direction end target before deviating from the most direct path to the target, the maximum distance travelled towards the forward direction end target, and the degree of postural stability while moving in the forward direction decreased. Moreover, there was a significant

positive relationship between H_{max} / M_{max} asymmetry and reaction time ($r = 0.518$, $p < 0.05$); which indicates that as reflex asymmetry increased so did reaction time. No other relationships were identified for the other three cardinal directions (i.e., backward, right, and left). Finding this relationship between reflex asymmetry and leaning in the forward direction did not come as a surprise as the soleus muscle is the primary muscle recruited to control balance while displacing the body's COG in the forward direction.

Asymmetries and Postural Control in MS

It is known that people diagnosed with MS tend to present with bilateral asymmetries across a range of measures (5, 28-30, 68), and that the majority of MS patients have some degree of balance impairments. While the soleus H reflex has been measured previously in MS patients it was either only collected in the right leg (63) or the most spastic leg (62) but not both. Therefore, to the best of our knowledge this was the first study of its kind in MS patients, and further illustrates the presence of bilateral asymmetries in people with MS.

Since balance and walking impairments is among one of the most challenging limitations in persons with MS (11) it is not surprising that a study in 2002 by Cattaneo and colleagues reported that 27 out of 50 (54%) participants reported falling at least once in the previous six months, and of those 32 percent were considered recurrent fallers having fallen more than twice (4). When matched for age, MS patients are injured two to three times more than people without MS as a consequence of falling (8). This has been suggested to be the consequence of a combination of reduced level weight-bearing activities compared to age-matched controls and the use of steroids for

symptom management, which can lead poor bone health and osteoporosis (11). Based on these statistics it is clear that falling is a significant concern for people with MS.

The current investigation used the SMART Balance Master to quantify postural control. The system utilizes a dual dynamic force plates that are equipped with rotational capabilities that measure vertical forces exerted through the participant's feet to measure center of gravity position and control of postural. The system also has a dynamic visual surround that measures the participant's use of visual input to maintain balance. Two different balance protocols were utilized in this investigation: 1) SOT, and 2) LOS. The SOT objectively identifies abnormalities in the participant's use of the sensory systems: visual, somatosensory, and vestibular. The LOS quantifies the maximum distance the participant can intentionally displace their COG in the four cardinal directions and the four diagonal directions while maintaining stability. The outcome measures associated with the LOS test are reaction time, movement velocity, endpoint excursion, maximum excursion, and directional control.

With the exception of SOT condition two, where the eyes are closed while standing on a fixed sway reference support (i.e., force plates) all six conditions were significantly different between groups in the present study (Table 9 and Figure 10). These results differ slightly from Fjeldstad and colleagues (2009) who only observed differences in SOT 1, 2, and 4 in a sample of relapsing-remitting MS (12). However, differences between our study and theirs could be attributed to the fact their sample of MS patients had a lower mean EDSS score than ours. Specifically, their MS patients had a mean EDSS of 1.6 and a smaller range (1 to 3) while our sample of MS patients had a mean EDSS score of 3.1 and a greater range of 1 to 6, which indicates more

disability. Moreover, Fjeldstad et al. (12) only enrolled relapsing-remitting MS patients while we had two participants with primary-progressive; a diagnosis that tends to have more disability. Indeed, the two primary-progressive patients in our study had an EDSS score of 5.5.

While it was not the main intent of the present study to specifically identify sensory dysfunction, but more or less determine if asymmetry in the soleus H reflex was correlated to balance control, the SOT quantifies sensory function in the vestibular, somatosensory, visual, or some combination of these three sensory systems. Using criteria by Nelson et al. (1995) a composite equilibrium score of 70 or less in any of the conditions indicates some degree of postural abnormalities (43). Condition 5 and/or 6 assesses vestibular function; conditions 4, 5, and 6 assess visual and vestibular function; and conditions 2, 3, 5, and 6 assess somatosensory and vestibular function (43). Of the eight MS participants in the present study six (75%) had equilibrium scores below 70 in condition 5 and three (38%) had equilibrium scores below 70 in condition 6, both of which indicate vestibular dysfunction. In contrast, only one (12.5%) non-MS participants had an equilibrium score below 70 (68.3) in condition 5 while all non-MS participants scored over 70 in condition 6. These results are similar to those of Nelson et al., 1995 where 57% of their low-functioning (a composite equilibrium score below 70 – none of our MS patients had a composite equilibrium score below 70) and 28.5% of their high-functioning MS participants had vestibular dysfunction (43) for a grand total of ~ 86% of their participants.

In a sample hemi-paretic patients that were within the first year after sustaining a stroke Oliveira et al. (2011) observed similar results to ours where they observed

significant differences in SOT conditions 3 through 6; however, their values for each condition were lower than ours (44). It is hard to say if their stroke patients were similar in disability to our MS patients, but it was reported that 33 percent of those enrolled had sustained at least one fall after the stroke, and they were on average less than six months post-stroke. Therefore, their level of disability could very well have been greater than that of the MS patients in the present study.

While other studies have assessed postural stability in MS patients, they did not use the SMART Balance Master system that was sed in the present study. For instance, Chung and colleagues collected vertical ground reaction forces using two adjacent force plates and calculated center of pressure variability in the anterior-posterior and medial-lateral planes, which was used as their measure of postural control (5). They also used their force plate data to determine bilateral distribution of body mass during 20 seconds of quiet standing, which has been unique to their study. The purpose of their study was to identify any relationships between these measures of postural stability and knee extension and ankle dorsiflexion torque and power asymmetry. Chung and colleagues observed a significant positive relationship between anterior-posterior COP sway and knee extensor power asymmetry, ankle dorsiflexion power asymmetry, and loading asymmetry scores ($r = 0.58$, 0.40, and 0.62, respectively). They also observed a significant positive relationship between medial-lateral COP sway ($r = 0.80$) and loading asymmetry.

The soleus H_{max} / M_{max} has also been used as a way to identify ankle spasticity in MS patients (63). Sosnoff et al. (2010) examined the spasticity's role in postural control in a sample of 16 MS patients. Degree of spasticity was determined by assessing

the soleus H reflex in the right leg where the high spasticity group had a H_{max} / M_{max} ratio of 0.80 ± 0.06 and the low spasticity group had a ratio of 0.43 ± 0.07. Sixty-three percent of our MS patients would have met the criteria used by Sosnoff and colleagues to identify spasticity, yet none of the MS patients in our study had been diagnosed with any degree of ankle spasticity. Similar to Chung et al., Sosnoff and colleagues collected center of pressure data using adjacent force plates to assess postural control. Balance assessments included postural sway, anterior-posterior sway range, and medial-lateral sway range (63).

H_{max} / M_{max} Reliability

In an attempt to provide the most reliable results possible only one tester collected all data. In support of this approach, our results for between limb H_{max} / M_{max} testing were very reliable between visits for both the MS and non-MS groups. Pearson's correlations were 0.98 and 0.93 for the left and right leg respectively in our non-MS group, yet were a little lower in the MS group, which was 0.92 and 0.89 for the left and right leg respectively. Within-limb intraclass correlation coefficients (ICC) were also strong for each group. Our non-MS group had ICCs of 0.97 and 0.95 for the left and right leg respectively, and our MS group had ICCs of 0.94 and 0.91 for the left and right leg respectively. These results demonstrate strong reliability in the H_{max} / M_{max} collected in the present study. Between limb reliability remained strong for our non-MS group ($r = 0.96$, ICC = 0.97, SEM = 1.39, but fell a small extent in our MS group ($r = 0.45$, ICC = 0.52, SEM = 5.87). When paired t-tests were run between visits for each limb only a significant difference was observed for the right leg in our non-MS group ($p < 0.05$, ES = 0.45), which is hard to explain since all recording and stimulating sites were outlined

with a permanent marker. All stimulation visits were performed at the same time each day to reduce day to day variability, and while we tried to control for before testing physical activity and caffeine consumption, the truth of the matter is some participants may have deviated from our protocol. Moreover, while the effect size is not as low as we would like, the value barely approached a moderate effect (ES = 0.45). Overall, our correlation coefficients and ICCs are in line with those previously reported on soleus H_{max} / M_{max} statistics (45).

CHAPTER V: CONCLUSIONS

The soleus H reflex was measured in both the left and right leg in a sample of MS and Non-MS participants to calculate Hmax / Mmax ratios. The Hmax / Mmax ratios were converted to an asymmetry score and correlated to balance performance. Significant differences were not observed between the left and right leg within each group, however, when the H_{max}/ M_{max} ratios were converted to an asymmetry we did observed differences between the two groups with the MS group displaying greater asymmetry. The two balance assessments used were the sensory organization test and limits of stability. The SOT consisted of six conditions and provided a composite equilibrium score. Only condition four was significantly negatively related to Hmax / Mmax asymmetry when the groups were pooled. The LOS test assesses an individual's ability to intentionally displace their center of gravity in eight directions; the four cardinal and four angular directions and calculates reaction time, movement velocity, endpoint excursion, maximum excursion, and directional control. We observed relationships while displacing COG in the forward direction in all measures except movement velocity; reaction time was the only positive relationship.

Answer to Research Questions

First Research Question and Hypothesis

Will soleus H_{max} / M_{max} ratio differ between limbs in a sample of MS subjects and healthy controls? It was hypothesized that the soleus H_{max} / M_{max} will differ between limbs in MS subjects, but will not differ between limbs in our Non-MS participants. We did not observe significant soleus Hmax / Mmax differences between legs in either the MS or non-MS group. The hypothesis that a difference in the soleus

H_{max} / M_{max} would be observed in our MS group was not supported by our data. The between-limb difference was 0.033 millivolts. However, our hypothesis that no differences in the soleus H_{max} / M_{max} would be observed in our non-MS group was supported by our data. The between-limb difference was 0.002 millivolts.

Second Research Question and Hypothesis

Following converting the soleus H_{max} / M_{max} ratios into asymmetry scores, will the asymmetry score be greater in MS subjects? We hypothesized the asymmetry score would be greater in our MS group. A significantly greater asymmetry score was observed in the MS group (21.7 ± 16.6 vs. 4.6 ± 3.9); therefore, the data supports this hypothesis.

Third Research Question and Hypothesis

Will the soleus H_{max} / M_{max} asymmetry scores be related to balance performance? We hypothesized the soleus H_{max} / M_{max} asymmetry scores would be significantly related to SOT and LOS performance. A significant relationship was not observed between our pooled asymmetry scores and the composite equilibrium score of the SOT. However, when the conditions were separated a significant negative relationship was observed between the pooled asymmetry scores and condition four, which consists of eyes open, a fixed visual reference, and a sway referenced platform. For the LOS test only relationships were observed between pooled asymmetry scores and the forward direction assessment. A positive relationship was only observed between reaction time and asymmetry scores. Negative relationships were observed between endpoint excursion, maximum excursion, directional control and asymmetry scores.

First Research Sub – Question and Hypothesis

Will Sensory Organization Test performance differ between our sample of MS and Non-MS participants? It was hypothesized that the composite equilibrium score would be significantly greater in the Non-MS group than the MS group. The composite equilibrium score was greater in the Non-MS group (85 vs. 80), supporting our hypothesis.

Second Research Sub – Question and Hypothesis

Will Limits of Stability test performance differ between our sample of MS and Non-MS participants? It was hypothesized that the Non-MS group would perform better in LOS testing; however, any specific direction was not stated. The results of the LOS test indicate the Non-MS group did perform better in LOS testing, however, it was only in the forward direction. Therefore, the data does partially support our hypothesis; unfortunately, our hypothesis lacked specificity.

Clinical Significance

It is known that bilateral asymmetries exist in people with MS, and that these asymmetries can have a significant impact in their daily life. Impaired balance is also a common consequence in people with MS, which has been shown to reduce their level of physical activity, as they tend to lose confidence in their ability to not fall, even in simple daily tasks such as walking. One area not fully understood was whether or not asymmetry in spinal reflexes existed in people with MS. More specifically, whether or not an asymmetry in the soleus H reflex – if present – would be associated with their ability to maintain balance during different balance tasks. The results of this study provide preliminary evidence of spinal reflex asymmetry and further support the notion

that bilateral asymmetries are common in people with MS. In contrast to previous research, this asymmetry was observed without exertion or motivation; both of which remove the influence of descending drive and the CNS. Moreover, asymmetry in the soleus H reflex appears to be significantly correlated with tasks such as leaning forward, and explains 50 percent of the variability in the ability to maximally displace COG in the forward direction ($r^2 = .50$). Since we are aware of this asymmetry, clinicians and therapist can work to improve this imbalance in the soleus H reflex as this reflex has been shown to respond to training and differs between populations (e.g., different athlete populations or young versus old). It is the hope that improving symmetry in this reflex may improve their ability to maintain balance when challenges are presented that displaces their center of gravity and lead to improved confidence and a more active lifestyle.

Future Directions

Now that it is known that the soleus H reflex can be asymmetrical in people with MS, it is important to begin designing interventions to address this imbalance. Therefore, future research should focus on training interventions to reduce asymmetry in the soleus H reflex, as well as tasks that improve balance. Further, since MS is a disease that directly affects the central nervous system, it would be interesting to investigate whether or not a variant of the H reflex – the V wave, which introduces the central nervous system and descending drive – is asymmetrical in people with MS as well. Since this was the very first study of its kind in people with MS, future research should investigate whether or not this asymmetry in the soleus H reflex is present in a second sample of people with MS. Finally, it may be important to replicate this study

with the exception of testing both the left and right during one visit to reduce day-to-day variability in not just reflex excitability but also daily fatigue in people with MS.

Limitations

As with any study the limitations associated with our 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 of them had large effect sizes. Also, these results are only representative of those who completed the study, which were 31 to 64 years of age. Six of MS patients in the present study did report a limb they perceived to be more affected, however, two reported that both legs were equally affected and since no other performance measure was collected between limbs comparing more affected to least affected was not possible. Another limitation is that the increase in stimulation intensity appears to have been too great resulting in the possibility for some of the H_{max} values recorded to be underestimated. When reflecting on the study design it may have been more important to test both legs in one visit to reduce any influence daily fatigue may have had on our stimulation results. However, we controlled for fatigue to the best of our ability using two common fatigue questionnaires. Finally, even though the SMART Balance Master is equipped with a parachute harness and overhead steel bar for safety reinforcement, we were not always comfortable strictly depending on it and at times of severe sway assisted the MS patients to reduce the likelihood of falling. This undoubtedly could have artificially enhanced some of their condition equilibrium scores, especially in the more challenging conditions (i.e., conditions 4 – 6).

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Appendix A: IRB Approval, Consent Form, and HIPAA

The UNIVERSITY of OKLAHOMA

Institutional Review Board for the Protection of Human Subjects

Initial Submission – Board Approval

Date: October 12, 2016

To: Rebecca D Larson, PhD

IRB#: 7169
Meeting Date: 09/26/2016
Approval Date: 10/12/2016
Expiration Date: 09/30/2017

Study Title: Relationship between Soleus H Reflexes and Balance Metrics in People with Multiple Sclerosis

Reference Number: 655611
Study Status: Active - Open - Expedited
Collection/Use of PHI: Yes

At its regularly scheduled meeting the IRB reviewed the above-referenced research study. Study documents (e.g. protocol, consent, survey, etc.) associated with this submission are listed on page 2 of this letter. To review and/or access the submission forms (e.g. application) 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 @ 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, OK

Relationship Between Soleus H Reflex and Balance Metrics in People with Multiple Sclerosis

Principal Investigator: Rebecca D. Larson, PhD
Sponsor: Department of Health and Exercise Science

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 are an appropriate age and gender matched control.

Why Is This Study Being Done?
The purpose of this study is to determine whether differences in an ankle reflex, known as the soleus (a muscle in your lower leg) H – reflex exist between legs. And secondly, to determine if there is a relationship between differences in your soleus H – reflex between limbs and balance measures. The soleus H – reflex is the electrical version of the stretch reflex that is traditionally assessed at a doctor's office, and requires application of both stimulating and recording electrodes (EMG electrodes). Electrical stimulation is unique to H – reflex testing, and is more than what is involved with traditional EMG measurements. Most importantly, the soleus H – reflex has been shown to relate to stability while standing, and individuals diagnosed with MS tend to display differences between legs which can negatively affect posture or balance.

How Many People Will Take Part In The Study?
About 30 people will take part in this study. All participants enrolled will be tested at the Department of Health and Exercise Science at the University of Oklahoma, Norman, OK.

What Is Involved In The Study?
This study will require a total of 6 visits to the Body Composition and Human Performance Lab. Total time commitment has been estimated to be 12 hours. The study involves measuring your soleus H – reflex in both legs to calculate a ratio of difference and relate the ratio to balance performance determined using three different balance tests. Measuring your soleus H – reflex requires specific preparation of your skin for placement of the stimulating and recording electrodes (explained under Visit 1). On the last visit (Visit 6) you will undergo three dual energy X-ray absorptiometry (DXA) scans (a full body and both hips) to determine body composition followed by three balance tests. These procedures are explained in greater detail in the following sections.

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 ask 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 to H-reflex, MVC, and Balancing Procedures: The purpose of familiarization with the H-reflex procedure is for you to become accustomed to electrical stimulation. A small stimulating electrode will be placed behind your knee and additional non-stimulating recording electrodes will be placed over your calf muscles. 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 prepped electrodes will be placed on your skin, and you will then be asked to lie on your back in the dynamometer (Kin-Com; Chattanooga, TN) with your knee and hip flexed at 90°. You will then receive a series of very brief electrical stimulations of progressively increasing intensities while force production and muscle activity are recorded. Electrical stimulation is unique to H – reflex testing, and is more than what is involved with traditional EMG testing. The number of stimulations you will receive is variable, but it is likely that you will receive between 100 and 200 shocks. The discomfort/pain experienced during this procedure varies between persons as a function of nerve anatomy, limb size, training history, and pain tolerance. Typically, the stimulation initially feels like a light pinch and gradually progresses to a stinging sensation similar to the feeling in your hand when you perform a very hard "high five".

Following H – reflex familiarization, and while still fastened to the dynamometer you will practice performing isometric maximal voluntary contractions (MVC) with your calf muscles. Essentially, you will be asked to press the ball of your foot into a fixed metal plate as hard as possible while attempting to lift your heel into the air while your entire foot is strapped down to prevent movement (similar to the motion when performing a calf raise exercise). Once you are comfortable with the movement, you will be asked to perform a series of 3 3-second MVCs separated by 3 minutes of rest.

Familiarization to the three balance protocols will be provided to finish visit 1. You will first be asked to remove your shoes before being fitted with a safety harness (similar to a rock climbing harness) that will catch you if you were to lose your balance. Once the

harness is securely fastened around your waist you will be asked to step up onto the NeuroCom® Smart Balance Master® System and align the outside of your ankle with the platform's axis of rotation. You will complete a minimum of one trial for each condition of the three balance tests, which include a Sensory Organization Test (SOT), a Limits of Stability (LOS), and a Unilateral Stance Test (UST). If you do not feel comfortable with a specific test or condition you will be provided additional trials until you are comfortable with the test. Each test is described in greater detail under the subheading "Visit 6"

Visit 1 will conclude end with scheduling your remaining 5 visits.

Visits 2 - 5

Visits 2 through 5 are intended to measure your soleus H – reflex to construct H – M recruitment curves in both limbs; each limb will be tested twice. The soleus is a muscle in your lower leg. Stimulation electrodes along with EMG electrodes will be placed in the exact location determined during the initial visit. Two responses are associated with the constructing a recruitment curve, the H – reflex and the direct muscle response (M wave). Stimulation will begin at 0.5 milliamps (mA) and gradually increase by 0.5 mA until a peak is observed in the H reflex amplitude (H_{max}) and a plateau is observed in the M wave (M_{max}). Stimulation intensities will be measured 3 to 5 times and averaged to create H – M recruitment curves. A minimum of 7 seconds but no more than 12 seconds will separate each pulse. We anticipate you will receive between 100 – 200 stimulations to construct each H – M recruitment curve.

Testing will take place in the same position as described during familiarization. It is important that a similar level of muscle activation exists between participants, therefore, visual feedback regarding your level of soleus activation will be provided during testing. The required amount of soleus activation must be maintained for 2 seconds for stimulation to occur. Rest will be provided every 30 minutes or when needed. Each visit in this block is estimated to last 120 minutes.

Visit 6

Visit 6 will begin with measuring your body weight and standing height using a standing scale. Both research and control participants will then undergo a full body and dual-hip DXA scans that allow us to measure the amount of bone, fat and muscle in your body. The full body scan takes approximately 10 minutes, and the dual-hip scan takes approximately five minutes.

After the DXA scan, you will be fitted to a safety harness used to catch you in the instance you start to fall during balance testing. You will then be asked to step up onto the testing platform and align your ankle with the appropriate reference point based on body height. You will then perform 3 different balance tests pre-programmed into the balance system. The assessments include the Sensory Organization Test, Limits of Stability, and Unilateral Stance, which now be described.

SOT consists of 6 conditions that will each be performed 3 times for a total of 18 balance scores. The platform that you stand on is referred to as sway reference support, and the 3

walls to your left, right, and in front of you are referred to as sway reference vision. All conditions are 20 seconds unless a fall is recorded. In the case of a fall the trial will be terminated and recorded as a fall.

Condition 1: you will be asked to stand quietly on a fixed (stable) platform and fixed surrounding walls.

Condition 2: same as condition 1 except your eyes are closed.

Condition 3: eyes open on the fixed platform, but surrounding walls move accordingly with changes in your body position.

Condition 4: eyes are open and the platform moves according to changes in your body position.

Condition 5: same as condition 4, except eyes are closed.

Condition 6: eyes are open, and both the platform and surrounding walls move according to changes in your body position.

LOS consists of leaning in 8 directions (forward-right, forward-left, backward-right, and backward-left). You will be provided visual feedback indicating your real-time body position. You will be provided 8 seconds to reach (and hold) each target direction.

The ULS test consists of standing on one leg with eyes open and eyes closed. The test determines your ability to maintain your posture while standing on one leg (both legs will be tested). The length of each trial will be 10 seconds, unless a fall is recorded during a trial. Each condition will be assessed twice, with one minute separating attempts.

How Long Will I Be In The Study?
We anticipate that you will be in the study for 2 to 4 weeks. There may be certain circumstances under which your participation may be terminated by the investigator without regard to your consent. These include failure to comply with investigators guidelines before and during each test visit. You may also be removed from the study if you have an exacerbation of symptoms related to MS.

You can stop participating in this study at any time.

What Are The Risks of The Study?
Radiation Risk from DXA
During the full body and dual-hip DXA scans, both research and control participants will be exposed to very low doses of radiation.
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.

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. A negative pregnancy test is needed prior to participating in this study. For unexpected pregnancies, subjects are encouraged to speak with their family physician. There is no cost to you for this test.

Maximal Contractions on the Kin-Com Dynamometer
While participating in the study you will be asked to maximally contract your 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 be screened for risk factors.

H – reflex Testing
On H – reflex testing days it is important that you refrain from taking any anti-spasm medicine until after testing, which may increase your risk of experiencing muscle spasms.

You will likely experience acute pain/discomfort resulting from the electrical stimulations applied during H-reflex testing. This pain/discomfort varies between persons, but is usually tolerable, quickly dissipates, and does not result in muscle injury or soreness. Typically, it initially feels like a light pinch and gradually progresses to a stinging sensation similar to the feeling in your hand when you perform a very hard "high five."

There may also be risks that are unknown at this time.

Are There Benefits to Taking Part in The Study?
There are no direct medical/health benefits from participation in the study. However, the information learned from this study will benefit those with multiple sclerosis in the future.

What Other Options Are There?
You may choose to not participate.

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 that may inspect and/or copy your research records for quality assurance and data analysis. These organizations include the US Food & Drug Administration, the University of Oklahoma Institutional Review Board, the OMRF

Institutional Review Board, and the OUHSC Institutional Review Board.

What Are the Costs
Due to requiring medical clearance for enrollment in the study there is a chance you will have to pay a fee to obtain your physician's or neurologist's signature.

Will I Be Paid For Participating in This Study?
For your time you will be compensated $100 upon completion of the study. If you do not complete the study you will receive $15.

What if I am Injured or Become Ill While Participating in this Study?
In the 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 the treatment. No funds have been set aside by The University of Oklahoma Health Sciences Center, the University of Oklahoma, or Oklahoma Medical Research Foundation 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. However, at certain times during the treatment, it may be dangerous for you to withdraw, so please be sure to discuss leaving the study with the principal investigator or your regular physician. 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 the 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.

Future Communications
The researcher would like to contact you again to recruit you into future studies or to gather additional information.

_____ I give my permission for the researcher to contact me in the future.

_____ I do not wish to be contacted by the researcher again.

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

IRB Office Version Date: 05/23/2014

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: **Relationship Between Soleus H - Reflex and Balance Metrics in People 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, soleus H - reflex testing, isokinetic/isometric dynamometer, and physical exams and findings.

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 spinal reflexes and how the differences relate to balance.

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)

[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.**

and the Department of Health and Human Services (HHS), and when required by law. The researchers may also share your PHI with no one outside the research team.

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: Rochester Fatigue Diary, Modified Fatigue Impact Scale, and Health History

Date: _____

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? **Y** **N**

   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**

Date: _____

About how much coffee, tea, or cola do you drink on an average day?

_____

_____

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? _____

Date: _____

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

Walking	Running	Bicycling	Swimming
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 your typical level of exertion during 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**

Date: _____

Relapsing remitting **Primary progressive** **Secondary progressive** **Progressive relapsing**

4. Briefly described your current MS symptoms _____
_____

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? **YES** **NO**

15. Has your physician ever recommended that you exercise? **YES** **NO**

Date: _____

Family Practice Physician _____ Phone _____

Neurologist _____ Phone _____

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 ____

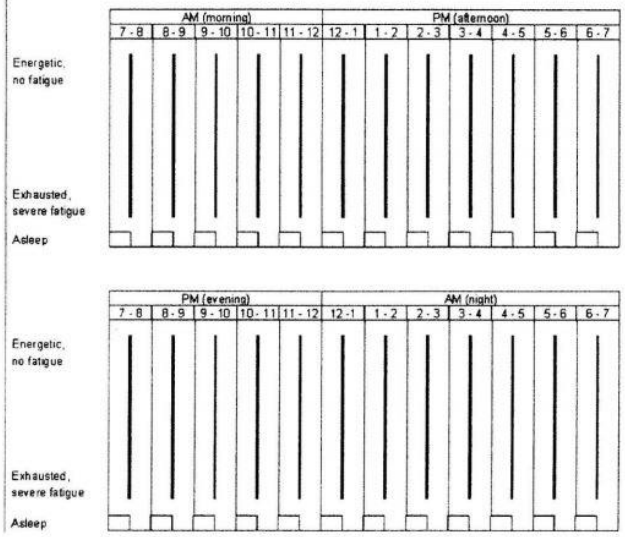
I certify that these answers are accurate and complete

_____ _____
YOUR SIGNATURE DATE

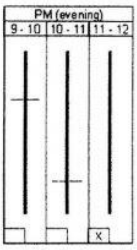
ROCHESTER FATIGUE DIARY

NAME: _____ DATE: _____

Instructions: Please mark a line each hour to rate your average energy level from energetic (high energy no fatigue) to exhausted (low energy, severe fatigue) during a 24 hour period (7 am to 7 am).



EXAMPLE:



The patient has recorded mild fatigue from 9 - 10 pm, substantial fatigue from 10 - 11 pm, and asleep from 11 - 12 pm.

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

Test#: 1 2 3 4 5 6 7 8

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. You may ask for clarification to 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: 7169
IRB APPROVAL DATE: 10/12/2016

	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:_____

IRB NUMBER: 7169
IRB APPROVAL DATE: 10/12/2016

Appendix C: Clearance Letters and Recruitment Flyer

The University of Oklahoma
DEPARTMENT OF HEALTH AND EXERCISE SCIENCE

Multiple Sclerosis Clearance Letter

Date _____

Dear Dr._____

A patient of yours,_____would like to participate in a study called, "Relationship Between Soleus H – Reflex and Balance Metrics in People with Multiple Sclerosis" which will be conducted at the University of Oklahoma. The goal of this study is to investigate bilateral differences in the soleus H – reflex and balance performance. Each testing/exercise session will be performed at the University of Oklahoma. Personnel experienced at working with individuals with MS will supervise all visits.

Your support of our MS research is very much appreciated. To comply with Institutional Review Board policy, we need a letter from you clearing your MS patient for participation in this study. Attached please find a copy of the research protocol and informed consent. Your written approval letter will include the subject's diagnosis, classification of disease and level of disability at study entry, and current medications. This letter indicates that you are aware of the testing procedures and the specific activities this individual will be performing. Participants will be included if they have an expanded disability status score less than 6.5 which reflects ambulatory status.

The individual participating in this research study will be advised to contact you if they experience any clinical symptoms between study visits.

Again, we greatly appreciate your support and request, at your earliest convenience, a response to this letter indicating your approval or disapproval of subject participation.

Rebecca Larson

Rebecca D. Larson, Ph.D., Principal Investigator
Department of Health and Exercise Science
College of Arts and Science
University of Oklahoma
Norman, OK

IRB NUMBER: 7169
IRB APPROVAL DATE: 10/12/2016

Diagnosis:_____ Initials:_____

Disability Status Score:_____ Initials:_____

Current Medications: Medication rationale (e.g., blood pressure):

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

Initials:_____

Additional Comments by Physician:

Please circle as appropriate: **APPROVED**

DISAPPROVED

Name of Physician:_____

Signature of Physician:_____

Date:_____

The University of Oklahoma
DEPARTMENT OF HEALTH AND EXERCISE SCIENCE

Non – MS Clearance Letter

Date_____

Dear Dr._____

A patient of yours,_____would like to participate in a study called, "Relationship Between Soleus H – Reflex and Balance Metrics in People with Multiple Sclerosis" which will be conducted at the University of Oklahoma. The goal of this study is to investigate bilateral differences in soleus H – reflex and balance performance. Each testing/exercise session will be performed at the University of Oklahoma.

Your support of our MS research is very much appreciated. To comply with Institutional Review Board policy, we need a letter from you clearing your patient for participation in this study. Attached please find a copy of the research protocol and informed consent. This letter indicates that you are aware of the testing procedures and the specific activities this individual will be performing. Your written approval letter will include a list of any current medications and the reason for the medication.

The individual participating in this research study will be advised to contact you if they experience any clinical symptoms between study visits.

Again, we greatly appreciate your support and request, at your earliest convenience, a response to this letter indicating your approval or disapproval of subject participation.

Rebecca Larson

Rebecca D. Larson, Ph.D., Principal Investigator
Department of Health and Exercise Science
College of Arts and Science
University of Oklahoma
Norman, OK

IRB NUMBER: 7169
IRB APPROVAL DATE: 10/12/2016

RESEARCH PARTICIPANTS NEEDED!!!

Relationship Between Soleus H – Reflex and Balance Performance in People with Multiple Sclerosis.

PI: REBECCA D. LARSON, PhD

TO PARTICIPATE

- MEN AND WOMEN
- 20 – 64 YEARS OF AGE
- INTERESTED IN LEARNING BODY COMPOSITION, ANKLE STRENGTH, AND BALANCE ABILITIES
- ANY ACTIVITY LEVEL

TIME COMMITMENT

- 6 VISITS
- 1-2 HOURS PER VISIT
- 2-3 WEEKS OF TESTING

REQUIRED TESTING

- PAPERWORK & FAMILIARIZATION OF TESTING (VISIT 1)
- ANKLE STRENGTH TESTING & H – REFLEX ACQUISITION (VISITS 2-5)
- BODY COMPOSITION SCAN & BALANCE TESTING (VISIT 6)

If you would like more information please contact:

Greg Cantrell
g.s.cantrell@ou.edu
(405) 479 – 9487
Department of Health and Exercise Science

The University of Oklahoma is an Equal Opportunity Institution. IRB 7169

Greg Cantrell g.s.cantrell@ou.edu 405-479-9487

Appendix D: DXA Physics Report

APEX MEDICAL PHYSICS

April 22, 2016

Debra Bemben, Ph.D.
Director, Bone Density Research Laboratory
Department of Health and Exercise Science
University of Oklahoma
1401 Asp Avenue, HHC Rm 104
Norman, OK 73019-6081

Dear Dr. Bemben:

On April 20, 2016, we completed the annual survey of your x-ray equipment. A report for each unit is attached. A summary follows.

1. Stratec PQ 3000 extremity computed tomography unit
   a. Radiation exposure to research subjects for the protocol tested with the Computed Tomography Dose Index (CTDI) adult head phantom, which is a good approximation for extremity scanning. The $CTDI_{vol}$ was determined to be 0.82 mGy and was measured according to the techniques specified in AAPM report No. 96. An effective dose of 0.08 uSv was calculated based on M J Braun, Phys. Med. Biol. 43 (1998) 2279–2294 where specific weighting factors for the anatomy and CT scanner involved are reported.

2. DEXA Unit - Room 2
   a. Radiation exposure to research subjects for the protocols tested results in the following effective doses:
      Spine Technique 1.70 µSv
      Femur Standard Technique 1.50 µSv
      Whole Body Technique 0.53 µSv

3. DEXA Unit - Room 4
   a. Radiation exposure to research subjects for the protocols tested results in the following effective doses:
      Spine Technique 1.83 µSv
      Femur Standard Technique 1.54 µSv
      Whole Body Technique 0.78 µSv

4. The QC procedures as recommended by the respective manufacturers for these units have been established. Results are within manufacturer specified limits.

All other aspects were found to be satisfactory. If you have questions about this report, please give us a call.

Sincerely,

Max D'Souza, Ph.D., DABR
Medical Physicist

3326 Fox Hill Terrace • Edmond, OK 73034 • USA
Phone: (405) 818-3750 • Fax: (888) 660-8858 • max@apexmedphysics.com • www.apexmedphysics.com