THESIS

LOWER-EXTREMITY ASYMMETRIES AND THEIR CORRELATIONS TO DISABILITY IN MULTIPLE SCLEROSIS

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ABSTRACT

LOWER-EXTREMITY ASYMMETRIES AND THEIR CORRELATIONS TO DISABILITY IN MULTIPLE SCLEROSIS

Maintaining balance and muscle strength are common areas of concern for individuals with multiple sclerosis (MS). Postural stability is associated with weight distribution asymmetries during quiet stance and leg strength asymmetries in people with MS. People with MS are also known to have higher levels of functional asymmetries compared to healthy people.

We examined asymmetry levels in people with MS during weight distribution in quiet stance and the sit-to-stand task as well as knee extensor and flexor strength asymmetries. We also identified associations between asymmetry levels and disability level, balance ability, and physical function.

Thirty-seven people (28 women) with MS completed the testing. Quiet stance trials were performed for 1 minute with each foot individually on a force platform. Maximal pace five-time sit-to-stand (5xSTS) tests were also performed with each foot on a force platform. Vertical ground reaction forces (vGRFs) were collected during all trials. Instantaneous center of pressure (COP) positions were computed during the quiet stance trials for assessment of postural stability.

Muscle strength of the knee extensors and flexors were measured via maximal voluntary isometric contraction on a customized knee extension machine. Participants pushed or pulled in 3-second intervals with ~2 minute rests in between until peak forces plateaued within 10%. The less-affected side was determined by symmetry index of the sum of knee extensor and flexor strength, unless strength symmetry index was within 10%, then self-report was used. Relative symmetry index (RSI) and absolute symmetry index (ASI) were calculated for the weight distribution and

strength measures between the more and less affected side. ASI was used for correlations between all variables. Repeated measures ANOVA was used to identify differences in RSI and ASI levels between average vGRFs during quiet stance and 5xSTS, peak vGRFS during 5xSTS, knee extensor and knee flexor strength. Pearson correlations were performed to examine associations.

Pairwise post-hoc comparisons of the ANOVA showed that knee extensor strength asymmetries were greater than 5xSTS vGRF average and max instantaneous asymmetries in both RSI and ASI sets. The 5xSTS ASI correlated highest with the balance and disability measures.

Based on these results, it appears that the expression of lower-extremity asymmetries are highly task dependent. As a result, no one test will suffice when assessing side-to-side differences in people with MS. However, if only one test is available, 5xSTS asymmetries may be more reflective of functional disability than those expressed during other tasks.

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For all the students graduating this semester, and for all the successful thesis defenses, for all the professors who keep the students mostly in line, for all the staff of the university for keeping this wonderful place operating; GO RAMS!

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INTRODUCTION

Multiple sclerosis (MS) affects one out of every 750 people in the USA and about 2.3 million people worldwide.[1] Damaged areas of the central nervous system from random immune-mediated and inflammatory attacks lead to poor neuromuscular activation, decreased motor function, and changes in muscle physiology downstream from the site of injury.[2,3] Symptoms from MS echo the anatomical location of lesion sites.[4] As a result, functional bilateral asymmetries in people with MS are present in greater levels compared to aged-matched healthy individuals in muscle strength[5], muscle power[5–7], aerobic performance[5,8], and weight distribution during quiet standing.[6] Functional bilateral symmetry may be indicative of a more symmetrical central nervous system.

Investigations on lower extremity asymmetries typically measure maximal isometric muscle strength or muscle power of the knee extensors and flexors[5,6,9], however it is not clear how these isolated joint tasks relate to functional measures of asymmetries and overall functional mobility in people with MS. Two common tasks, quiet standing and sit-to-stand are ubiquitous in our daily lives and require both balance and strength. Quiet stance assesses static balance more than strength whereas sit-to-stand transitions test dynamic balance and functional strength.[10–12]

In older adults, weight distribution asymmetries during quiet stance are associated with instability, possibly as a compensatory mechanism due to a slowed nervous system, lack of fine motor control, and reduced muscular strength.[13] While a weight distribution asymmetry may comprise postural stability, it is possible that an asymmetric stance may aid in a quicker step response if balance is lost.[13] People with MS often experience similar symptoms of delayed neural conduction,[14,15] poor balance,[1,15,16] and muscle weakness[1,9] however it is unknown if the MS

population compensates for imbalance with asymmetrical stance analogous to the elderly or for other reasons.

The maximal pace five-times sit-to-stand (5xSTS) test has been used as a clinical measure in a wide range of populations for assessing muscular strength, balance, functional independence, and asymmetries in weight distribution and strength.[11,12,17–21] In people recovering from knee replacement surgery, weight distribution asymmetries during the 5xSTS test relate to poor functional mobility and quadriceps strength asymmetry.[11] The time to complete the 5xSTS test has been shown to relate to lower body muscle strength and balance ability in individuals with MS.[10] Maximal knee extension power asymmetries during the sit-to-stand transition have been shown to be present in people with MS who exhibited leg extensor weakness.[7] However, asymmetries during the 5xSTS test have not been examined relative to other task asymmetries or disability levels in people with MS.

The goal of this investigation was to examine lower extremity asymmetries in a population of people with MS within the context of balance, physical function, and disability level. We hypothesized that weight distribution asymmetries during quiet stance and the 5xSTS would be similar in magnitude to each other and similar to knee extensor and knee flexor strength asymmetries. We also hypothesized that these asymmetries would be correlated to each other within the sample population. Finally, we hypothesized that these asymmetries would be correlated to 5xSTS time to completion, balance ability, and other measures of physical function and disability level. This information will be helpful in rehabilitative therapies for addressing bilateral imbalances. Knowledge on the bilateral symmetry of strength and weight distribution during functional tasks may result in improved rehabilitative efforts for individuals with MS.

REVIEW OF LITERATURE

Introduction to MS

Multiple Sclerosis (MS) is an inflammatory disease, primarily affecting the brain and spinal cord of the central nervous system (CNS). There are various forms of the disease, each with differing symptoms and pathologies, and along with the inherent heterogeneity of MS, clinical manifestations can be widely different between individuals. MS has a lifetime risk of 1 in 400 and currently affects about 400,000 people in the USA and has been diagnosed in over 2 million people worldwide.[4,22] It is also the most common neurological disease in young adults.[23] Life expectancy after diagnosis is >25 years and most die from unrelated causes.[4]

The exact cause of MS is still unknown, but it is believed to involve both environmental and genetic factors, primarily affecting those in northern Europe, middle North America, and southern Australia.[4,24,25] Women are twice as likely to be diagnosed with MS compared to men, similar to most other autoimmune diseases.[4,24] Although people of all ethnicities are affected by the disease, MS has a higher prevalence among Caucasians.[1] Unfortunately, no single gene has been identified to be linked to the disease. MS is frequently diagnosed during young adulthood with symptoms lasting several days, followed by spontaneous or drug-induced regression.[24] The primary treatments for MS are pharmacological drugs used to slow progression and diminish rate of relapses, but they are unable to repair damaged tissue.[22]

Some of the most common symptoms of MS are poor balance and weakness.[1] One of the earliest signs of MS is poor balance which greatly affects walking and activities of daily living.[26,27] Muscle weakness also plays a large role in MS and can cause early fatigue during normal tasks, greatly disturb locomotion, and may alter quality of life for many of the people living with the disease.[1]

Typically, the disease affects one side of the body more than the other, often leading to functional asymmetries.[9] These asymmetries can negatively affect activities of daily living, requiring a greater effort to accomplish daily tasks and leading to more fatigue.[28] In non-MS populations functional asymmetries are linked to increased disability level and poor functional performance.[17]

This review will cover the characteristics and functional deficits of multiple sclerosis as it contributes to asymmetry, postural stability, strength, and sit-to-stand transitions. The aim is to reveal why people with MS are predisposed to developing asymmetries, point out the documented asymmetries in the MS literature, and discuss why they affect the motion and daily life of those with the disease. First, the forms, symptoms, and pathology of MS will be overviewed in order to gain a better understanding of the disease. Next, the balance and postural stability characteristics of people with MS will be examined. Third, strength and the sit-to-stand test will be discussed as they relate to MS. Finally, we will discuss asymmetries as they pertain to balance and strength, how they affect this population, and how they have been reported in the literature.

Overview of MS: Types, Symptoms, and Pathology of the Disease

MS Types and Stages

Before diving into the specific characteristics of MS it is important to note that there are various forms of the disease, each with different symptoms, clinical courses, and pathologies. In the mid-1990s Lublin and Reingold noticed that there was a lack of clarity and much confusion on which type of MS was being discussed and documented in the literature.[29] This led them to consensually define the clinical course and phenotypes of the disease by polling leading scientists and clinicians involved with MS. These initial definitions were readily accepted by clinicians and researchers alike and recently, in 2014, there was an update of newer revisions clarifying initial

queries.[30] The three types of MS (Figure 1) put forth by these experts are relapsing-remitting (RRMS), primary-progressive (PPMS), and secondary-progressive (SPMS).[29,30]

Relapsing-Remitting MS

RRMS constitutes: "clearly defined disease relapses with full recovery or with sequelae and residual deficit upon recovery; periods between disease relapses characterized by a lack of disease progression", as described by the initial definition from Lublin and Reingold in 1996.[29] RRMS presents in ~80% of people with MS at onset of the disease.[4,24] After being diagnosed with this form, most people will spend several years in RRMS, going through phases of disease activity (relapse) and inactivity (remission) before advancing into the secondary-progressive phase (SPMS), discussed below.[31] Relapses begin over a period of a few days, peak, and then diminish over several days to weeks. The affected regions depend on which site of the brain has been targeted. Although relapse episodes happen randomly, they initially occur about once per year with the frequency tending to decrease thereafter.[4] Relapses will be discussed in more detail in the pathology section of this review.

Primary-Progressive MS

The disease may begin in a progressive phase, known as primary-progressive (PPMS)[31], defined as: "disease progression from onset with occasional plateaus and temporary minor improvements allowed".[29] PPMS is much less common than RRMS, only present in ~ 20% of the diagnosed population. People with PPMS do not experience relapses and have little to no signs of lesion activity when analyzed by MRI. They witness gradual decline of function primarily due to spinal cord involvement, atypical to other forms of MS.[32] A rare sub-form of PPMS is known as progressive-relapsing MS, described as "progressive disease from onset, with clear acute relapses, with or without full recovery; periods between relapses are characterized by continuing progression".[29]

Secondary-Progressive MS

SPMS is exemplified by "initial RRMS disease course followed by progression with or without occasional relapses, minor remissions, and plateaus".[29] RRMS can transition into SPMS; however, there has yet to be a clear sign (clinical, imaging, immunologic, or pathologic) determining the transition point.[30] The two progressive forms of MS are not considered to be inherently different in terms of pathology, but rather as a part of a range, once again due to the variable manifestations of the disease. PPMS is understood to be a portion of a larger spectrum of progressive MS, inherently having relative rather than absolute or definitive differences and likely having similar pathophysiological features as SPMS.[30]

Clinically Isolated Syndrome

Some people with MS may present a clinically isolated syndrome (CIS), presenting inflammatory demyelinating characteristics that could be MS, but not yet fully meeting criteria for MS (i.e. no second symptomatic event nor MRI confirmed activity). CIS may or may not develop into full MS at a later time since full classification of MS warrants two separate relapses. However it has been shown via MRI that people even with just CIS have irreversible inflammatory damage.[33]

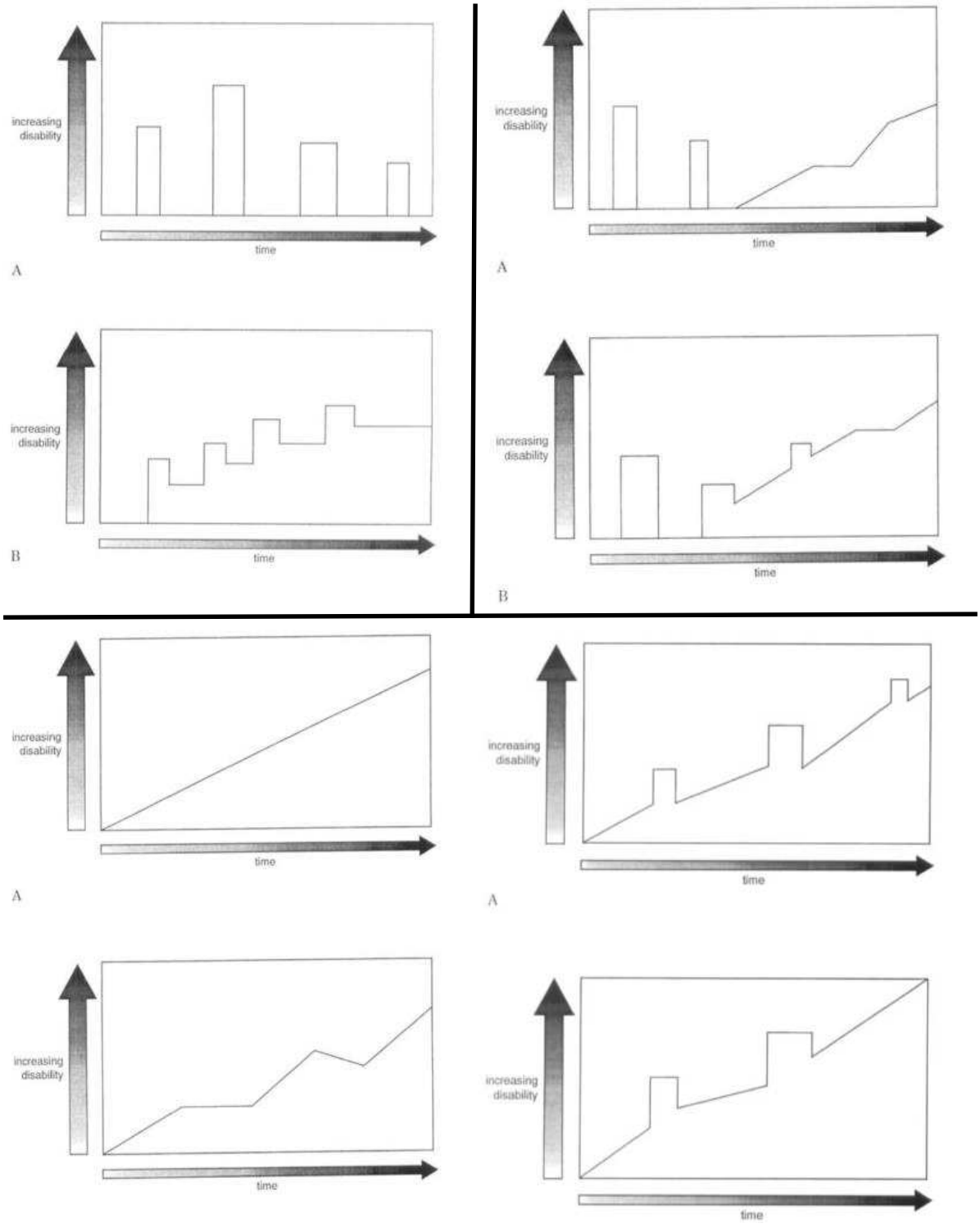

Figure 1*: Graphical representations of the 3 subtypes of MS from Lublin and Reingold, 1996.*[29] *RRMS (top left) is constituted by spontaneous relapses with no disease progression in between. SPMS (top right) begins as RRMS, but then progression begins eventually with or without additional relapses. PPMS (bottom) initiates as slow disease progression only, and in rare cases may involve relapses. All graphs contain time on the horizontal axis and disability level on the vertical axis.*

Is

MS Only One Disease?

The fact that separate forms of MS tend to affect different populations with discrepant prognoses, inconsistent lesion prevalence, contrasting immunopathology, and varying symptoms raises the question whether these forms are the same disease.[4,34] MRI and clinical studies have assessed the symptoms of each phase and have found that there are key differences between the stages, especially in terms of diagnosis, pathology, and treatment.[35–37] Some of these findings are: less cerebral involvement in PPMS versus SPMS[4], and generally higher levels of inflammation are found in SPMS than PPMS.[34]

Grouping the phenotypes of MS can be done by A) disease activity or relapses that defined by imaging techniques of the CNS seeking clinical signs of relapse occurrence and B) progression of disability status over time. Based on these definitions, RRMS and progressive forms are exclusive of each other and should be treated differently in the clinic. However they are somewhat related in the fact that RRMS often leads to SPMS, but researchers have had difficulty identifying and quantitatively describing this transition point.

Symptoms of MS

One reason for the difficulty treating and studying MS is that individuals experience differing symptoms which depend on the anatomical location of lesions and the type of MS.[38] Disease activity (lesions in RRMS) are considered acute symptoms while disease progression (PPMS or SPMS) is referred to as a chronic symptom.[30] In RRMS the unique person's symptoms reflect the location of affected sites: the neurological deficits are due to impaired axonal conduction at the anatomical/functional from local demyelination.[4] Due to more widespread effects, it has been difficult to integrate functional neurological deficits with specific lesions with MRI studies in progressive MS.[39–41]

Symptoms of RRMS may range from any of the following: visual loss, unilateral optic neuritis (inflammation of the optic nerve), double vision, limb weakness, paralysis, paresthesia (tingling and pricking), sensory loss, clumsy or slowed gait, psychiatric disorders, bladder and bowel issues, and dementia.[24] Rare symptoms originating from cerebral cortex, brainstem, or extrapyramidal dysfunction are: apraxia (poor motor planning), aphasia (disorder of language cognition), recurrent seizures, loss of vision, dementia, chorea (abnormal involuntary movement), and rigidity.[24]

In progressive multiple sclerosis (SPMS or PPMS), symptoms have a gradual onset and slowly worsen with time.[24] These symptoms may include: cognitive impairment, dysarthria (speech impairment from motor dysfunction), depression, vertigo, dysphagia, progressive quadriparesis and sensory loss, pain, sexual dysfunction, ataxic tremors, spasticity, and other CNS impairments.[4,24]

One symptom that is present across all types of MS is fatigue from demanding cognitive and physical tasks, requiring a longer recovery following demanding tasks than the average person.[4,42,43] Fatigue is present in about 80% of the population, can be triggered by heat and humidity, and typically worsens throughout the day.[1] It is likely a multifactorial symptom, can be very disabling, and may potentially lead to other issues in chronic cases.[4] However, fatigue is difficult to measure in experimental studies, because there is no way to consistently quantify fatigue levels between people because it is largely a subjective symptom.

The abilities affected by MS that have been rated most valuable by people with the disease are lower limb function/mobility[22,44] and secondarily, vision[44], showing that independence and ambulation are most important to this population and should be the target of most experimental studies and rehabilitative programs. This is separate from the symptoms that are mainly

responsible for reduced quality of life in people with MS which are fatigue, pain, spasticity, and depression.[22]

A general symptom in MS is weakness to a greater extent on one side of the body.[9] However, only recently have asymmetries been studied in MS, with documented asymmetries in strength[5], muscular power[5–7], bone mineral density[45], glucose uptake[28], and oxygen uptake.[5,8] These are the first reports of asymmetries in the MS population and will be further discussed later on in this review. However, even with this small sample of literature, it is clear that asymmetries do occur in the MS population and should be studied in greater detail.

Classifying Disability Levels of MS

Chronic disability level is determined by two factors: incomplete recovery following relapse and disease progression.[4] As expected, disability level correlates highly with disease duration, especially in progressive forms. However, lesion size and amount correlate weakly with disability status.[46]

Although many types of disability classifications exist, the main scale used specifically for MS is the expanded disability status scale (EDSS) created by Kurtzke in 1983.[47] This scale combines a neurologist's scores on the functional systems based on the origin of disability (pyramidal, cerebellar, brain stem, sensory, bowel & bladder, visual, cerebral or mental, and other/miscellaneous).[47] The EDSS was created to simplify the comparisons of disability level between people with MS, before which each separate functional system had to be compared rather than one overall score that combined the attributes of each system. EDSS is by far the most used disability scale available.

However, the EDSS has its demerits: variability between raters, requires a certified neurologist to administer, a non-uniform representation across grades, and can be unresponsive to progress.[48] Due to these reasons, Hohol et al. devised another method to evaluate disease

progression among people with MS, the disease steps (DS).[48] Instead of rating the various affected systems and their severity, the DS rates functional outcomes relating to motor dysfunction and ambulation, leading to simple and quick classifications.[48] DS has been validated against the EDSS with a correlation coefficient of 0.958 (n = 1,323), higher interrater agreement (kappa coefficient = 0.80 DS vs 0.54 EDSS, n = 60), and a uniform distribution whereas the EDDS classification resulted in a bimodal distribution.[48] Longitudinal relevance of the DS scoring system was evaluated[49] and found to be reliable and valid when following people with MS over time. Although DS was a simpler and quicker assessment, it still requires a physician to administer.

A patient-determined DS scale (PDDS) that does not require a neurologist was developed to further facilitate classification of disability level.[50] This scale has also been validated against the EDSS, with varying significant correlation coefficients ($r = 0.958$[50], $r = 0.783$[51] and $r = 0.64$[52]). Currently, PDDS is commonly used due to its ease to administer and ability to be completed without a neurologist present. Other scales have also been developed, however none have been as widely accepted as EDSS and PDDS.

Pathology of MS

The Relapse: Lesions and Plaques

A relapse is defined as: "An acute episode of new disease activity, either a new lesion or fresh activity in an old area of involvement."[29] RRMS lesions typically cause a set of symptoms, depending on the affected area in the CNS, which will peak within 2 or 3 days, plateau, and then decline over a few weeks.[53] This indicates that the lesion size is established shortly after the onset of symptoms.[53] As stated before, the patient may or may not fully recover following the relapse, and any residual symptoms following the relapse will likely become permanent. Rarely, a relapse can be fatal in which early MS death is caused by rapidly worsening disease or from isolated brainstem/upper spinal cord lesions.[24,53]

Lesions (damaged areas of tissue) are found in CNS white matter, the location where nerve impulses are relayed between locations in the brain. These lesions originate from autoimmune attacks from T-lymphocytes, activated macrophages, microglia, and antibodies.[54] These cells attack oligodendrocyte cells (and other cell types) degrading the myelin sheath surrounding nerve axons (demyelination) and sometimes causing axonal damage.[31,36] Demyelination is primarily witnessed in the cerebrum and cerebellum[31,55,56], and may reach up to 100% in the lesioned area depending on the severity of attack.[55] Interestingly, total lesion load and disability level have weak to modest correlations, likely due to both limitations in classification and effects outside the brain, namely the spinal cord.[57] An overview of the mechanisms leading to demyelination and inflammation are shown in Figure 2.

Just as there are various types of MS, there are also diverse types of lesions; which may portray variable amounts of inflammation, demyelination, astrocytosis, and axonal damage.[57] Not only are the localizations of each lesion different between individuals, but demyelination patterns are also different between MS types.[38] Partially demyelinated axons experience a reduced velocity of action potential propagation, causing delays in neuron signaling.[4] Fully demyelinated axons may spontaneously discharge and/or show higher mechanical sensitivity.[4] Progressive MS exhibits higher numbers of lesions in deep indentations of the cortex and cerebellum [31,55] Beyond the initial injury, there may be additional disease activity at the edges of inactive plaques.[58]

Chronic plaques, or the remaining tissue following a lesion, typically are fully demyelinated and may have inflammation (or other disease activity) near the edges.[57] However re-myelination after an immune attack may occur in variable amounts.[57,59] Cytokines along with growth–promoting factors are released from astrocytes and microglia to promote remyelination.[4] Re-myelination is slowed by gliosis and astrocyte reactivity sealing the lesion.[4] This re-myelinated

region is called a shadow plaque, which may still have local inflammation, but axonal injury is typically less pronounced.[58]

Axonal Damage from MS

In the late '90s, Ferguson[36] and Trapp[23] highlighted the clinical importance of axonal injury in MS, before which was widely thought to only affect glial cells. Amount of axonal loss among MS lesions is highly variable not only between people, but also between lesions, with axonal damage ranging anywhere from 20 to 100%.[60] This damage manifests itself as atrophy and decreased density of axons in affected brain tissue. Thick axons are better preserved compared to thin ones.[61] Axonal injuries occur secondary to inflammation of surrounding tissue (oligodendrocytes and astrocytes) and may be acute or chronic depending of severity of attack.[31,36] Axonal damage has been shown to occur in CIS (earliest manifestation of MS) with widespread and potentially irreversible axonal damage.[33]

In 2002, Compston and Coles proposed that axonal loss is not due to inflammation, but rather due to loss of support from surrounding glia (myelin-creating cells and others).[4] This rationale is sound in the fact that it is the glial cells that are primarily being attacked by inflammation and the immune response, and it is the job of glial cells to support the neurons: without glia, neurons cannot survive. However, this theory has yet to be proven experimentally.

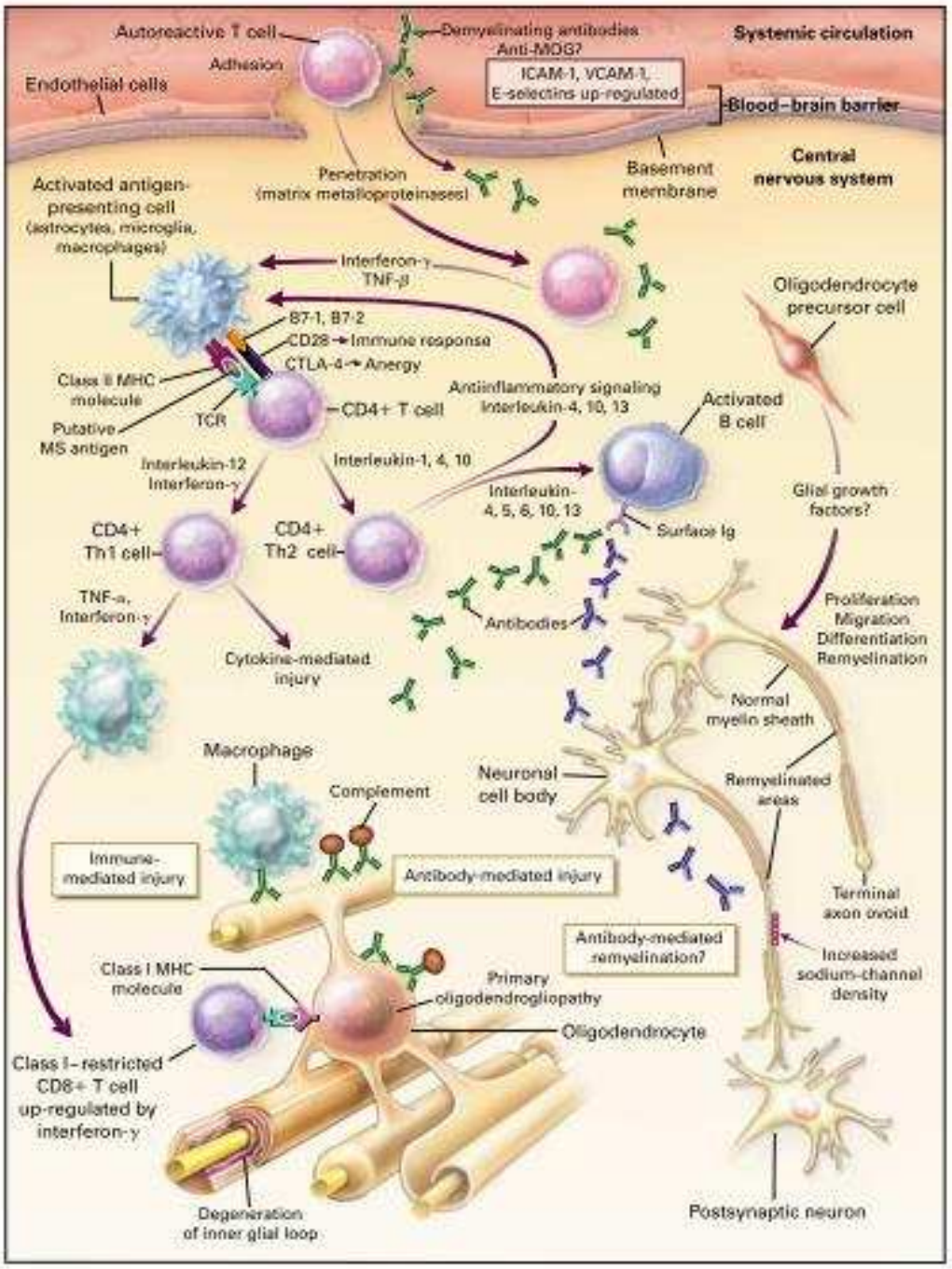

Figure 2: *Overview of the mechanisms leading to demyelination in the CNS. From Noseworthy et al. 2000.*[24]

Pathological Effects of Progressive MS

Although the two subtypes of progressive MS begin differently, clinical deterioration is similar between PPMS and SPMS.[37] The main differences between PPMS/SPMS and RRMS are

time course and location of affected areas. Local inflammation and white matter lesions in the brain constitute RRMS while widespread inflammation is more representative of progressive MS (PPMS and SPMS). CNS degeneration in progressive MS is slower and ongoing rather than rapid and intermittent in RRMS. The whole brain and/or spinal cord is affected concurrently and chronically in progressive MS[56] compared to the localized regions in RRMS. Both PPMS and SPMS are associated with widespread axonal injury in normal-appearing white matter.[56] Diffuse injury in the normal-appearing white matter can be profound even with a low level of total brain lesions,[56] which can have lasting neurological deficits.[62]

Conclusions and Future Directions

MS is a heterogeneous disease, with radically different manifestations of neural dysfunction. Now that the various forms of the disease have been adequately described, researchers are working to identify specific areas of each form to address. MRI protocol variations are beginning to be able to parse out the components of the underlying pathologies of MS, including inflammation, demyelination, astrocytosis, and axonal damage. This will lead to new pharmacological and functional treatments to reduce disease severity in the future, thus improving quality of life and functionality of current and future people with MS.

Balance and Postural Stability in MS

One of the most common symptoms of MS is poor balance. This has been quantified copiously while many researchers and clinicians seek to identify interventions to improve balance and reduce fall risk. Maintaining balance during daily life is paramount to remain fall free and reduce the risk for injuries. Balance is an important skill not just for people with MS, balance impairment is ubiquitous in the elderly.[63] In this section we will discuss how a person maintains

postural control, how to measure balance, and the balance deficits that exist among the elderly and MS population.

A Few Definitions

When discussing balance, there are a few terms worth defining in the ensuing paragraphs to ensure understanding of jargon in this context. The *center of mass* (COM) is the location of the weighted average of all masses of the body in 3D space, or the single point at which a person's weight can be localized, and can change depending on positioning.[63] For example, raising an arm to grasp something to one's front will move the COM both up and forward. Simply, if we control our COM, we control our body. The *center of pressure* (COP) is the weighted average of all pressures in contact with the ground and is separate from the COM.[63] Even though the COM and COP are entirely different entities, they are highly related and COP is commonly used to assess balance characteristics in quiet stance situations.[64]

Posture is the orientation of a body segment relative to gravity.[63] To maintain posture would be to maintain a body orientation in line with gravity. The term, *balance*, is a universal term to describe the dynamics of posture used to maintain an upright position or the sum of inertial forces acting within and upon the body.[63] During quiet standing a person *loses balance* when their COM moves outside the base of support.[65] Because humans are not stationary, but free to move about space they must actively maintain their static and dynamic posture using balance.

Latency is the time required to sense, process, decide, and act upon a response to a perturbation. In normal and healthy people the latency for muscular response after loss of balance is around 70-110 milliseconds.[14,66] *Excursion* or maximum voluntary excursion is the individual's maximal shift of the COP within the base of support.[65] This is similar to lean or *sway*, except that sway technically deals with the COM rather than its two dimensional projection, COP. Because the COM and COP track nearly identically in quiet stance, they are interchangeable in this context.

COP and COM movements can be quantified in the anterior-posterior (front and back) and the medial-lateral (left to right) directions. Typically, greater fluctuations are seen in the anterior-posterior (AP) direction compared to the medial-lateral (ML), however this depends on the width of support. When stance width is narrower, there is more instability in the ML direction.[15]

Functional Components of Postural Control and Recovery Strategies

Maintaining balance necessitates the ability to predict, detect, and encode the characteristics of active and passive disturbances.[66] This is the sensory component of postural control. Of course, to be able to respond to a postural perturbation, one must sense that they are falling. There are 3 sensory systems used by the CNS – visual, vestibular, and somatosensory.[63] Naturally, the visual system includes the eyes and optic nerves and integrates graphic information from the environment to help determine motor output to stay upright. The vestibular system can be thought of as the body's own 'gyro', sensing linear and angular fluctuations. The somatosensory system encompasses the proprioceptive and contact/pressure sensors in the periphery that relay signals back to the brain. Balance also requires the capability to choose and adapt a corrective response, and successfully implement that choice.[66] This is the motor component of postural control. If a person cannot favorably act upon the perturbation to balance, upright stance will be difficult to maintain.

Indeed, these two systems are inseparable, sensory input leads to motor output, which changes our orientation with the environment, leading to new sensory information to decipher. All while this is happening the CNS is gathering the sensory information, processing its relative importance, identifying potential motor outputs, and choosing the best strategy to correct the posture. These groups, sensory input, motor output, and the central processing between the two, make up the systems model and the functional component approach of postural control.[66] All three

systems are important not only to maintain balance, but also to choose the correct strategy to recover from lost balance.[67] Selection of recovery strategy seems to be an automatic process that is dependent on the sensory information available.[67] Without these systems, or improper function of these systems, balance and postural control will be affected.

Postural responses can be initiated in two ways: following an unexpected and external perturbation, or, more commonly, in anticipation of voluntary movements and actions to prevent from loss of balance occurring.[66] When one's balance is disturbed, a decision must quickly be made on how to deal with this perturbation. In quiet standing, three types of balance recovery strategies commonly exist – ankle, hip, and step strategies (Figure 3).[66] Selection of strategy depends on the disturbance and the abilities of the individual. The ankle strategy is typically the first choice of recovery method used to shift the COM and involves movement about the ankle with minimal movement elsewhere in the body.[66] The hip strategy involves large movements of the pelvis and/or torso to reposition the COM to a more stable position.[66] The stepping strategy is

Figure 3*: Examples of the three types of the most common movement strategies for correcting AP sway: ankle, hip, and step (from left to right). From Horak et al. 1989.*[66]

the last resort to maintain balance and adjusts the base of support to the perturbed COM position with steps, hops, or stumbles.[66]

Assessing Postural Stability

Here we will review various methods of assessing balance during quiet stance. Plentiful balance tests exist, both static and dynamic, however we will review those only that specifically deal with a standing in place and without physical locomotion (stepping) required to complete the test. This list will not be exhaustive due to the sheer number of tests, however the most common examinations will be discussed below.

Balance Tests and Equipment

Stabilometry is the most simple of balance tests, measuring center of COP or COM movements over time while standing quietly. Although simple, it provides substantial information on maintenance of stationary postural stability. However this type of test may not be highly reflective of one's ability to prevent a fall since most falls occur during transitions or perturbation rather than during quiet standing. Stabilometry is typically performed with force platforms, however accelerometry and motion capture have also been used.[68,69] For this type of test, minimal movements of the COP/COM would result in better balance while greater amplitude and frequency of sway composes poor balance. This test can be made more complex by requiring specific foot positions or by performing a task such as reaching with the upper body towards an object or voluntarily swaying back and forth.[70,71] Maximum leaning/reaching can also be quantified via a functional reach test.[26,72]

More difficult balance tests involve maneuvering the COM of a person and recording the movements to regain balance. This has been performed by manipulating the individual's COM or the ground beneath them. Moving platforms have been used to perturb participants and measure the motor response to correct posture, initiating one or multiple abrupt movements to deter

balance.[14,73,74] In these scenarios, the platform typically moves in the AP direction to initiate sway or stepping. Foam pads during stationary Stabilometry have been used to increase the difficulty of postural stability. These pads act to decrease the effectiveness of postural stability responses and proprioceptive inputs.[68]

There are numerous foot positions that can alter the postural control strategy or increase difficulty: normal stance, feet together, tandem feet (one in front of the other), 45 degree position (intermediate between normal and tandem).[75,76] As the foot placement changes from normal, hip and ankle postural control strategy changes with respect to AP and ML stability and the muscle groups responsible for control.[76] In addition to the various two footed positions, balance can also be tested on one foot and be compared between sides. In addition to foot positioning, stance width can be altered during these trials. As stance width decreases, base of support also decreases, and difficulty to maintain the position increases. Feet together would be the narrowest bipedal stance width and most difficult one to maintain. Many authors use 4 or 10 cm[16,77] as a universal width while others ask the participant to stand in a comfortable position with feet shoulder width apart. Furthermore, foot splay, or the angle between the feet can be altered during standing trials. However, this is rarely used among custom postural stability tests.

It is very common to assess the visual feedback used during balance[15,75,78], by closing one's eyes during the task. The visual feedback is by far the easiest system to exclude during balance or motor tasks. However, researchers have successfully negated the effects of the other two systems experimentally. Somatosensory feedback has been nullified by vibration of the musculotendinous unit, which acts to overload the proprioceptive muscle spindles with information and activity so that they fail to communicate the correct muscle length during a task.[79] Vestibular feedback, arguably the most difficult to exclude, has been voided during a balance task by having a stationary

standing person manually control a load with their feet that was matched to their own standing physical properties (same COM and mass).[80]

Analyzing Balance Data

Once the balance test has been accomplished, there are still various manners to analyze the data. Most balance data deals with COM or COP positions over a period of time. When analyzing kinematic data, COM movements are recorded and fluctuations in movement or sway distances are calculated. When force platforms are used with kinetic and pressure data, the COP is used to determine balance ability. As mentioned above, the COP is not the same as the COM, but it can be used to identify fluctuations in movement.

There are several common variables used to quantify the COM or COP movements of postural stability. The first is sway or the range of the furthest excursions of the COM/COP in opposite directions. A greater sway distance, or larger movements of COM/COP movement from the base of support, indicates poorer balance.[77] Sway area has also been computed during standing balance trials to measure balance by multiplying the AP and ML distances to derive an area of which the COP has been located.[81,82] Sway area has also been computed as an elliptical area that encompasses all or most of the COP movements over time.[83] Another method is by looking at the variations of the COM/COP compared to the average. The standard deviation of the COM position is known as the variability of the COM/COP. The root mean square has also been used to measure variability in sway patterns.[84] Total path length of all the movements of the COP has also been used to quantify balance – where a longer length signifies poorer balance.[81] Finally, the maximum velocity of the COP is used to quantify postural stability, where larger maximum velocities signify poor balance.[74] Naturally, there are more ways to analyze balance, however the above variables are the most commonly assessed and most simple to quantify.

Due to the wide scope and wealth of literature on the topic, balance in elderly people will now be discussed to obtain a general idea of balance deficits and how they may arise. Studies in elderly people have found deficits in various physiological systems that control postural stability: vestibular, somatosensory, visual function, neural motor pathways, central processing, and musculoskeletal soundness. Aging can solely account for significant changes in postural stability by incorporating any of the above deficits.[66]

The elderly have poor postural stability compared to the young and healthy because they cannot estimate their COP position as precisely and they have larger oscillations of the COP near the borders of stability.[65] The maximum voluntary excursion is a measure of how far one can position their COM/COP in a direction, very different from a static stance trial. Greater maximum voluntary excursions would signify a greater ability to move the COM/COP toward the limits of stability. In the AP direction, the maximum voluntary excursion (similar to COP sway) for the elderly consists of only 50% of the base of support, but it can reach 80% of the base of support for the young.[65] In the ML direction the elderly have a maximum voluntary excursion of 68% of their base while the young can use 80% of their base of support.[65] This shows a large reduction in the space for the stability area. A larger area for the COP/COM to move within would result in less loss of balance and decreased use of the strategies to maintain it. However, a reduction in the base of support area may be compensatory due to a reduced reaction time. This reduction in the functional base of support allows for a higher probability of recovery from instability by allowing more time to perform a recovery strategy.[65]

Balance Deficits in People with MS

Poor balance in MS is marked in a myriad of manners. Substandard postural control has been quantified across the whole spectrum of disability in people with MS, from no disability at

early onset to high disability after decades of living with the disease.[26,72,75,77] Pathologies that slow down voluntary movements may cause delays in postural responses.[66] Approximately one-half of people with MS report a fall within the last year.[85] By improving balance, the hope is that falls decrease among the MS population and overall quality of life improves. The main balance-related parameters found to be altered from MS are listed below.

People with MS sway more than healthy controls in the AP[6,15,68,77,86] and ML[83,87] directions during quiet stance. AP sway results from instability at the ankles whereas ML sway occurs due to abductor and adductor activity at the hips.[66] Both AP and ML sway would be affected by reduced proprioception, decreased neural transmission velocity, and compromised CNS processing. There is also an increased sway area among the MS population.[81–83,85] Higher disability levels correlate with larger amounts of sway.[68,69,85,87] A longer path length was also documented in people with MS versus healthy controls.[81] Karst et al. 2005 found that individuals with MS that have minimal disability were unable to voluntarily move their COP as far as healthy, age-matched controls during a maximum lean and reach task.[72] Martin et al. 2006 found similar results during the functional reach test also in a low disability MS group.[26] Huisinga et al. 2014 showed that postural response latency is longer in MS compared to controls thus it takes more time to elicit a motor response which can lead to greater instability and more falls.[74] These measures demonstrate that people with MS have clear issues maintaining balance in quiet stance.

Soyuer et al. 2006 quantified balance across the different types of MS by timing how long individuals could maintain specific positions up to 30 seconds and concluded that SPMS and PPMS had worse balance than those with RRMS.[75] Fritz et al. 2014 also found poorer balance and walking velocity measures among PPMS and SPMS compared to those with RRMS.[71] This concurs with the fact that most individuals experiencing progression of the disease have a higher

level of impairment and disability for a variety of reasons. One of those reasons is cerebellar dysfunction, which was noted to be higher among people with progressive MS (PP and SP) compared to those with RRMS.[75]

The balance tests that best discriminate between healthy and MS populations are tandem stance, single limb stance, functional reach, and external perturbation tests.[16] Path length and velocity of the COP were found to be the best balance variables that distinguish between healthy and MS groups, however this was observed during trials without visual feedback.[88] Cattaneo et al. 2008 found that people with MS are able to successfully weigh sensory inputs and select a strategy to maintain performance of balance.[88] Regardless, a reduction in the amount of sensory information available leads to large increase in sway and number of falls.[88]

Sosnoff et al. showed that spasticity affects postural control in people with MS, documenting greater ML sway, sway area, and velocity of the COP during quiet stance in people with MS with high levels of spasticity compared to low spasticity and heathy controls.[83] Spasticity refers to the continuous contraction of muscles due to CNS dysfunction. It is prevalent among people with MS, causing chronic muscle stiffness and tightness affecting gait and other activities of daily living.

Balance measures have often been investigated along with strength and walking characteristics and this is no different in the MS population. Poor balance has been shown to greatly affect gait speed.[6,15,71] There are also other symptoms of MS that affect gait, namely strength and fatigue. Although the MS population is highly known to be susceptible to fatigue throughout the day, Frzovic et al. found that they had very consistent balance performances between morning and afternoon sessions.[16] However, Hebert and Corboy, 2013, found that symptomatic fatigue is highly related to balance and can predict balance outcomes.[89] Taken

together, perhaps it is the individual's susceptibility to fatigue that alters postural stability, rather than onset of fatigue from daily function. Strength measures among people with MS will be discussed later in this review.

Proprioceptive Loss in MS

The compensation of visual dependency in MS is due to loss of somatosensory and vestibular function.[69] The somatosensory system has been shown to be primarily responsible for deficits in the MS population. Delayed proprioceptive feedback is related to postural instability,[14] when proprioceptive feedback is altered or slow, large deficits in balance can occur. Motor delays as short as 20 milliseconds can cause destabilization.[66] The muscle spindles, which sense proprioception via minute muscle length changes, are likely not the initial source of the proprioceptive inabilities of MS, but rather it is the transmission and processing of those signals in the CNS that account for poor proprioception.[79]

When somatosensory inputs from the lower legs were the only afferent allowed (blocked visual, vestibular, and somatosensory below the ankle) during standing posturography, Fitzpatrick et al. 1994 found that muscle afferent or proprioceptive feedback from the lower leg was sufficient to maintain standing balance among healthy subjects.[80] This highlights the importance of proprioceptive muscle spindles, and that one can maintain balance relatively well with only this area of somatosensory feedback. Cameron et al. 2008 looked at somatosensory conduction in the spinal cord and supraspinal regions and their contribution to balance. They that found that people with MS had significantly longer spinal somatosensory evoked potentials (17.2 ± 8.1 ms MS vs 7.9 ± 1.8 ms control, $p < 0.01$), prolonged latency (response from lost balance), and a greater predictive response to external perturbations.[14] Postural response latencies correlated with the slowed spinal somatosensory transmissions.[14] With a longer postural response latency in MS versus controls, those with MS must have larger responses to return their body from the unbalanced

position. These longer latencies are due to slowed afferent proprioceptive conduction, not a delayed motor response. Similar latencies were found in Huisinga et al. 2014, who also documented significant correlations between COP sway and postural latencies, yet it is likely not the only factor.[74] Fling et al 2014 used MRI diffusion imaging to find white matter tracts affecting the proprioceptive pathways in the human brain.[82] Microstructural integrity of the proprioceptive tract had poorer quality in MS and was related to proprioceptive balance control in both MS and control groups.[82] They speculated that since cortical proprioceptive tracts were affected, postural stability may be limited to use of visual, vestibular, and cerebellar proprioceptive tracts.

Poor balance in static and dynamic situations has been attributed to cerebellum and brainstem involvement, also being largely affected by fatigue and abnormal central sensory integration.[69,89] Prosperini et al. 2011 found more lesions in the middle cerebellar peduncles and brainstems in fallers compared to non-fallers with MS using MRI techniques.[90] However they did not find any clear relationships between disability level, cerebellar areas, balance deficits, or fall risk.[90] They attributed these null findings to potential spinal cord damage that likely contributes to balance deterioration. The poor balance seen in those with MS is different from aging-related balance issues. In aging, the deficit could be due to a wide range of factors, however with MS, it is primarily the last of somatosensory feedback that leads to poor postural control.

In summary, the balance deficits due to MS are seen in anticipatory postural adjustment, sensory feedback, and gait.[82] This is present in people with MS during quiet stance with greater COM/COP movements compared to healthy controls. The deficits are also present in perturbing balance tests with longer response times to correct posture in people with MS compared to healthy individuals. These deficiencies can be due to combinations of impaired proprioceptive feedback, poor central integration, and visual dependency. Improving the balance of people with MS may

result in a lower prevalence of falls, an improvement in disability level, a greater ability to perform activities of daily living, and improvement in quality of life.

Strength and the Sit-to-Stand Task in MS

Sit-to-stand tests are primarily a measure of lower body strength, and decreased strength is one of the hallmark symptoms of MS. The effects of MS on muscle tissue and the CNS/PNS regarding strength will be reviewed before discussing the sit-to-stand task.

Central and Peripheral Nervous System Effects on Strength

Deficits in strength are understood to be due to impaired conduction in CNS pathways that have been demyelinated.[91] This reduces the ability for the PNS to be activated, thus causing motor neuron recruitment and/or firing frequency issues downstream from the lesion. Chronically, this may lead to muscle atrophy and deterioration due to disuse, leading to a snowball effect of further weakness and additional inability to perform daily activities.

Rice et al. found that people with MS could not maximally activate their muscles, not all motor units can be recruited voluntarily, and motor neuron firing rates during maximal contraction are reduced compared to normal.[91] Poor motor unit recruitment and reduced maximal discharge rates from CNS impairment likely results in large variability and overall lower amount of strength in people with MS.[3,91] Initial firing rates to activate motor units in people with MS were much lower than the firing rates of the normal population, and the frequency required to activate 50% of a muscle was also lower in some people with MS compared to controls.[91] Ng et al. found that slow rate of voluntary force development in MS and muscle weakness was primarily due to CNS impairment, where the disease activity takes place.[2] They speculated that PNS deficits were secondary to CNS deterioration and reduced muscle activity.[2]

Widespread changes in skeletal muscle likely also have a great effect on the reduced strength witnessed in MS, with documented strength deficits in MS from 15 to 50% weaker than controls on average.[9,81,92] This wide range of differences may vary with the muscles being tested (primarily knee extensors and flexors) and the disability level of the group(s). Strength testing in MS groups has reliably and consistently shown them to be weaker than control groups.[42] Motor fatigue is separate from muscle weakness in MS, as fatigue level has no association with degree of weakness in individual muscles.[42] Spasticity and stiffness may also affect the strength and muscle twitch properties of MS. The muscle characteristics of individuals with MS, in terms of fiber type and size, more closely resemble muscles of spinal cord injury patients than those with disused muscles.[3]

In general, muscle fiber area is reduced by ~25% compared to healthy controls.[3] People with MS had a lower cross-sectional area of type 1 (slow twitch) muscle fibers and greater area of type 2a (fast twitch) muscle fibers compared to healthy.[3] These statements seem somewhat contradictory, since type 2 muscle fibers are generally larger and stronger than their type 1 counterparts, however the decreased overall muscle size (area) is likely due to the CNS deficits described above, while the fiber type oddities may be described by the energy pathway changes described below.

People with MS likely have a greater reliance on anaerobic energy pathways in muscle.[3] Recovery of phosphocreatine levels post-exercise is slowed compared to healthy controls, showing impaired oxidative capacity in people with MS.[93] Lower amounts of the oxidative enzyme succinate dehydrogenase, part of the oxidative energy pathway, correlate with low physical activity levels in MS and healthy groups.[3] However, Kent-Braun at al. also showed that muscular

fatigue was not related to changes in energy metabolism, though they speculated that MS causes changes in muscle activation during contractions.[94]

Sit-to-Stand

Breaking down the STS Movement

The STS movement can be thought of as 4 distinct actions[95], beginning with normal sitting and ending with upright stance. Phase 1 of the movement, or the flexion-momentum phase, involves trunk and/or hip flexion and acts to initiate the forward movement of the body's center of mass (COM). Phase 2 is referred to as the momentum transfer phase and begins when the buttocks rise from the chair and lasts until maximum ankle dorsiflexion occurs, mostly acting to translocate the COM anteriorly. Phase 3, or the extension phase, begins at max ankle dorsiflexion and extends until hip joint extension halts, consisting of primarily of raising the COM to the standing position. Phase 4, the stabilization phase starts with the termination of hip extension and finalizes once all postural corrections are completed. The stabilization phase may be nearly instantaneous among healthy or low disability-level people. Initial momentum for the upward and forward acceleration from the sitting position is provided by forward flexion of the trunk in order to anteriorly displace the center of gravity within the supporting area for the rest of the standing movement.[64]

The Sit-to-Stand Task in MS

The sit-to-stand (STS) task originated in the mid 1980's as a 10-repetition task for simple assessment of lower extremity muscle strength throughout the lifespan.[96] More recently, STS transition tasks are still commonly used to assess balance and lower extremity strength, typically to identify fall risk in elderly or motor disabled populations.[97,98] It is a popular clinical and research test due to simplicity, requiring minimal equipment, ability to be performed in a variety of settings,

and translation to daily activities. STS is mainly used as a predictor of functional mobility, independence, and quality of life among elderly and disabled populations.[98]

While the test does not directly measure balance or muscle strength, but rather time to completion, five-time STST (5xSTS) performance has been shown to have strong correlations with knee extensor strength[21] and also balance ability.[12] Because this test is an indirect measure of muscle strength, it is useful to measure the impact of strength on daily function.[99] The 5xSTS has been used in a wide variety of populations including healthy adults[100], the elderly[101], osteoarthritic individuals[102], and those recovering from joint replacement surgery[17], amputees[103], and people with neurological disorders such as stroke[104], Parkinson's Disease[105], and MS.[7,10]

When the individual does not have a sufficient strength capacity to perform the sit-to-stand task in a normal manner, a new strategy is developed – called the trunk flexion strategy. It is difficult to determine how much force is being produced by the working muscles during the 5xSTS, but we can assess their performance capacity via movement strategies. Muscle weakness has been replicated among a healthy population by adding weighted vests to the subjects and comparing normal and weighted trials.[106,107] The increased load led to the adoption of the trunk flexion strategy, which reduces loading moments about the knee while increasing hip joint extension moments.[106] Lower body muscular strength was found to be the strongest predictor of the sit-to-stand movement in the elderly.[21] The trunk flexion strategy has been linked those with muscle weakness.[7,106,107]

Bowser et al. (2015) identified strategies of people with MS compared to controls during the sit-to-stand task. They found that the MS group used the trunk flexion strategy to account for deficits in leg strength, they took longer to complete the test, they produced less power during the task, and the authors speculated that the MS group used a larger percentage of their maximum

strength to accomplish the test.[7] The differences between the healthy and MS groups were primarily due to leg extension weakness, where they saw a significant reduction in one-repetition max leg press between both MS groups and controls (MS with leg weakness 1.18(0.15) was less than both MS with comparable strength 1.91(0.50) and healthy control 2.13(0.56) x body weight, $P \leq 0.003$).[7]

In comparison to balance and direct strength tests, STS tests have been rarely performed on people with MS. This is surprising for two reasons. First, STS is an indirect measure of strength, but is also dependent upon balance ability and both of these factors are impaired in MS. Second, the STS is a very simple test to perform, only requiring a stopwatch and a normal chair. It is very useful in clinical settings and is very transferrable to daily functions. For these reasons, the STS should be used more in the MS population and may provide additional insights into balance and strength than just testing either ability separately.

Associations between Balance and Strength

Outside of MS, there have been numerous studies on balance and strength, and nearly all of them found that muscle weakness is an important and consistent factor for maintaining balance (Figure 4).[99] Of course the neural pathways to sense orientation and cause movement are important to maintain stability, but the action of muscles are the "ultimate effector" in this dynamic system.[99] Without the muscles, there is no movement and no balance to maintain.

Although both balance and strength deficits in MS have been quantified heavily, there are only a few studies that seek to identify the relationships between these functions. Citaker et al. found that strength in most of the major muscle groups of the lower limb (hip flexors, extensor, abductors, and adductors; knee extensors and flexors; and ankle dorsiflexors) were all related to single leg balance ability in people with MS.[92] All these tests were performed on the dominant side

(kicking leg) and they also correlated with disability level (EDSS).[92] Chung and colleagues reported knee extensor strength asymmetry correlating with postural stability in people with MS.[6] Yahia et al. found a correlation between hamstring peak torques (on both sides) and sway area during the eyes closed condition.[81] Balance, strength, and asymmetries will be discussed further in the upcoming section.

All of these studies suggest that improving muscle strength, or strength symmetry, may improve balance ability in people with MS. The relationship between balance and strength in this population may be due to improving central and thus peripheral neuron activity and motor unit recruitment.

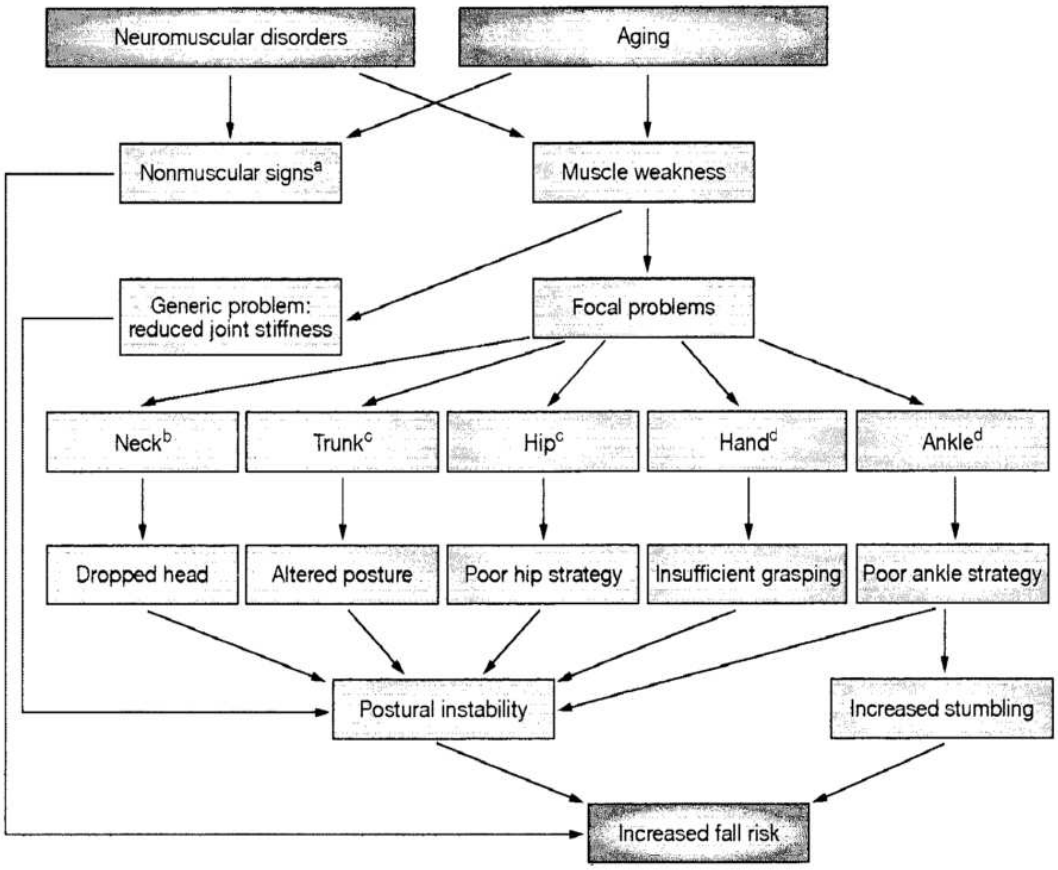

Figure 4: *Theory of interactions between falling and muscle weakness as it pertains to the elderly and those with neuromuscular disorders. The authors showed here that falls, weakness, and balance are related, yet different entities. From Horlings et al. 2008.*[99]

Balance, Strength, and Other Asymmetries in MS

While strength and balance related characteristics have been heavily documented in the MS literature, there are very few studies looking at asymmetrical relationships between these topics. In MS, though random, generally one side of the body is more affected and thus weaker than the other.[9] This may cause greater risks for falls during locomotion and daily activities and may impair balance response. Prior research has focused on the pathophysiology and characteristics of the disease but not on the laterality of its symptoms, which has been shown to have an effect on functional mobility in other populations.[11] Interestingly many studies have mentioned that they are aware that asymmetries may play a role in this population, especially among RRMS, but only few have specifically tested this issue. In this section we will review this small body of literature and show why asymmetries are important and should be further studied.

Presence of asymmetries in MS is happenstance solely due to the random chance of lesion location.[38] Currently it is unknown why certain regions of the CNS are targeted by the disease, while other areas are left relatively unharmed.[24] Investigations in this area may prove fruitful to potentially prevent future attacks, unfortunately it doesn't look like this will be feasible in the near future. In the meantime, we can look at the asymmetry of the person's functional abilities to determine disability level and identify therapy interventions to maintain ambulation and independence.

How do asymmetries begin and why do they matter?

The demyelinative and axonal damaging effects of MS have a large influence on what symptoms are displayed by the individual, including affected limbs. For example, if the individual experiences a lesion in the right hemisphere at the location of the motor cortex controlling the right leg, then they will likely have motor dysfunction in their left leg from improper axonal

communication beginning at the site of the lesion. When the disease affects the dominant side of the body, many daily activities become more difficult and potentially dangerous. Asymmetries may also affect the metabolic cost of performing daily activities such as walking, potentially causing fatigue earlier than normal.[28] This fatigue from asymmetrical function may also add or contribute to the predisposition of fatigue in the MS population.

Typically, asymmetries indicate an impairment in function and are often measured to assess risk of injury in rehabilitating patients and fall risk in the elderly. However, many healthy people do display functional asymmetries in normal activities such as: jumping[108], landing[109], squatting[110], and cycling.[111] These asymmetries in the healthy population may begin due to habitual tendencies or side dominance. Asymmetries due to disability are very common in populations suffering amputation[103], hemiparesis[18,97], spinal cord injury[112], orthopedic injuries or disorders[11,17,113], and chronic muscular or connective tissue injuries such as low back pain.[114]

In people with MS, Chung et al. (2008) discussed the relationships between knee extensor strength asymmetries with balance, gait, and fatigue.[6] In Figure 5, these relationships are displayed, showing that strength asymmetries may be a main mediator for the other three. The authors suggested the strength related therapeutic interventions may help in improving the physiological, functional, and symptomatic issues of people with MS.[6] This is one of the first published examples of asymmetry in the MS population.

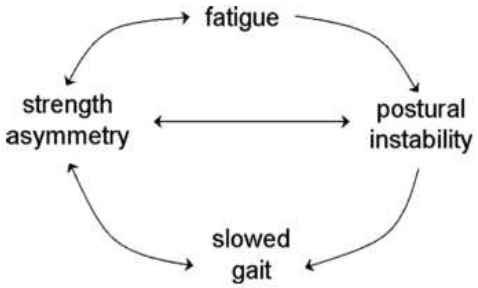

Figure 5: *The effects between strength asymmetries, fatigue, postural instability, and slowed gait. From Chung et al. 2008.*[6]

Measuring Asymmetries and Side Dominance

There are various ways to measure asymmetries when presented bilateral measures. One simple way to look at this difference is by testing whether a bilateral difference exists via student's

t-test. Another method is by measuring overall percent difference. For example, if the left side measures 30 and the right measures 40, then there is a 25% difference between sides $D = 100\% * (1 - \frac{Lower}{Higher}) = 100\% * (1 - \frac{30}{40}) = 25\%$. This is the same as symmetry ratio[115], which is determined by: $R = \frac{(R-L)}{\max(L,R)} * 100\% = \frac{40-30}{40} = 25\%$. Asymmetry score has also been used to quantify loading asymmetry during quiet standing: $Asymmetry\ Score = \left(\frac{High}{High+Low}\right) - \left(\frac{Low}{High+Low}\right) = \left(\frac{40}{70}\right) - \left(\frac{30}{70}\right) = 14.3\%$.[6] A final way to measure asymmetry is by symmetry index (SI)[115,116]: $SI = \frac{R-L}{0.5(R+L)} * 100\% = \frac{40-30}{35} = 28.6\%$. One limitation and benefit of SI is that it uses the average of the two sides to determine asymmetry. This may cause asymmetries to be measured differently than other methods as seen above, but it also takes both sides into account to determine that difference, yielding a more concrete asymmetry score than just comparing one side to the other.

Some studies will report an asymmetry value without noting the dominant side. Losing function on dominant side may cause symptoms different than those from dysfunction on the non-dominant side, even in the general population. This may even progress to the "dominant" side switching to compensate from motor symptoms of the disease. Side dominance can be determined by self-report, questionnaire, or observation.[115] In healthy people, this is often settled by asking which side they would to prefer to use to accomplish some task (self-report). For the arms, writing or brushing one's teeth are commonly used. For the legs, the side chosen for kicking a ball or initiating gait is convenient. Additionally, questionnaires exist to parse out the right from the left in this case, asking about many more activities and summing all the tendencies in to one to generalize their laterality.[117] Finally, one can observe how people perform tasks to record side dominance. This can be done by vaguely asking them to do various tasks and noting the side in

which they choose to perform it. Observation of side dominance can also be determined by having a subject do a task unilaterally for each side. This is commonly done in strength testing and other functional tasks such as dexterity or aerobic function. In this dual measure method, one can record and analyze the bilateral deficit and compare between populations.

Weight Distribution and Balance Asymmetries

Asymmetries in weight distribution or limb loading are commonly seen among those with poor balance. During quiet standing, weight distribution asymmetries were found in the elderly which also correlated to postural sway with eyes closed ($r = 0.72$, $P = 0.005$).[13] Weight distribution asymmetries were noted among the elderly during a sit-to-stand task.[19] Weight bearing asymmetries during sit-to-stands are also common in patients recovering from joint orthoplasty.[11,17]

Standing asymmetries should be considered a functional asymmetry that incorporates bilateral differences in anatomy and deficiencies of the postural system from aging and pathology.[13] Weight distribution has been shown to affect standing postural control. Chung et al. reported a greater loading asymmetry score between people with MS and controls (10.5 (6.9) vs 6.0 (3.0), $p = 0.05$) and the asymmetry was associated with both AP and ML variability of the COP.[6] However knee extensor and dorsiflexor peak power differences did not affect limb loading.[6] The asymmetrical stance adopted by people with MS may be due to a wide range of factors. If weight distribution is not even, perhaps one limb is primarily controlling posture as well, while the other may be preparing for a step strategy recovery as demonstrated in the elderly.

Blaszcyzk et al. showed that elderly people had an approximate 7% asymmetrical weight distribution during quiet stance with eyes open.[13] When visual feedback is taken away in elderly, limb loading asymmetries increase compared to eyes open, reinforcing the preferred stepping limb

strategy.[13] They also showed that age and vision significantly contribute to weight bearing asymmetry and are associated with increased postural sway.[13] The compensatory responses that cause asymmetrical limb loading are long lasting or permanent postural manifestations.[13]

Maximum voluntary excursion was found to be asymmetrical between right and left sides with a right-to-left ratio of 1.17, or a further right side lean than to the left (Figure 6).[65] The maximum voluntary excursion ratio of anterior to posterior was heavily forward at 1.76, or a much further lean forwards (Figure 6).[65] In this study the elderly showed a difference in their ability to lean backward and to the left compared to young people. In the elderly, leaning forward and to the right were similar to the young. In theory, an asymmetrical maximum voluntary excursion would create an asymmetrical stability area.[65]

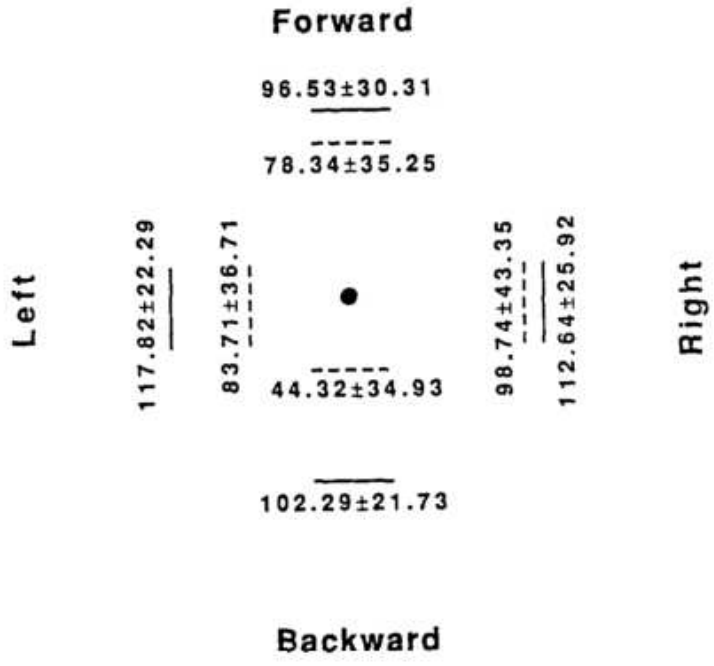

Figure 6: *Maximum voluntary excursion asymmetries in the elderly compared to young. Values from the elderly are in dashed lines while the young are solid lines. The elderly are unable to voluntarily move their COM as far as the young in the backward and left directions, however are able to do so in the other two. From Blaszyczk et al. 1994.*[65]

Blaszcyzk et al. proposed that the limb loading asymmetry is a compensatory mechanism to reduce the time required to take a step to regain balance.[13] This marks a change in the recovery strategy from the ankle method commonly used among young and healthy subjects to the stepping strategy for the elderly population. The ankle and hip strategies of balance recovery seek to act symmetrically to maintain the

COM within the base of support. The step strategy's effectiveness may be enhanced by an asymmetrical stance, making it easier to take a step to recover from a self-initiated or non-external postural disturbance.[13] This may explain the increase in asymmetrical stance with age and MS.

Strength Asymmetries

The most documented asymmetry among people with MS is in strength, perhaps first documented by Rice et al. in 1992.[91] Strength asymmetries have been found to affect balance, fatigue, and gait.[6,28] Strength measurements in people with MS have been found to be reliable, even though their strength measures tend to be lower compared to healthy controls.[9]

When measuring strength and power asymmetries in women with MS, Chung et al. found that AP instability during quiet stance correlated with knee extensor and dorsiflexor power asymmetries ($r \geq 0.40$, $P \leq 0.05$) and loading asymmetries ($r = 0.62$, $P = 0.001$).[6] Larson et al. also reported an overall bilateral difference in strength (43.3(12.7) kg strong vs 37.7(15.2) kg weak, $P = 0.004$), peak workload (73.4(22.3) W strong vs 56.3(26.2) W weak, $P = 0.01$), and peak oxygen uptake (13.7(3.2) mL/kg/min strong vs 10.6(3.0) mL/kg/min weak, $P = 0.002$).[5] Lambert et al. used dynamic strength measures at a variety of speeds and found slightly greater peak torque asymmetry of knee extensors and flexors in MS compared to controls, but not statistically significant.[9] Absolute and relative (normalized to fat free mass) peak torque production was lower among people with MS versus controls for the non-dominant knee extensors and flexors and also the dominant flexors.[9] Only dominant side knee extensors were similar between groups, perhaps showing that compensation in activities of daily living may offset the effects of the disease.

Asymmetries in STS

Schofield et al. found that healthy populations do have ground reaction force (GRF) asymmetries during the 5xSTS movement and express lateral favoring (asymmetries) at the ankle and hip joints.[118] However the favored side cannot be predicted by limb dominance alone and the

levels and laterality of asymmetry were highly variable between trials and participants. This demonstrates that even among healthy people, asymmetries in the 5xSTS movement are present and that lateral favoring may be separate from side-to-side dominance. This interaction may be further complicated in people with MS when disease affectedness comes into play. In people with MS, asymmetries have not been studied during sit-to-stand trials, so it is currently unknown how this population performs these tests in terms of asymmetries.

In people recovering from unilateral knee replacement, Christiansen et al. found that greater weight bearing symmetry during a 5xSTS is associated with more symmetrical quadriceps strength.[11] Thus vertical GRF asymmetry during a 5xSTS may be a good target for strength, balance, and asymmetry testing in people with MS.

Other Asymmetries

After 15 minutes of walking, asymmetric glucose uptake was found in the hip flexors and knee flexors of low disability people with MS.[28] With similar exertion levels between healthy and MS groups, greater glucose uptake levels were also found, likely indicating higher levels of muscle fatigue. Knee flexor maximum voluntary contraction strength was found to be dissimilar between sides.[28] In tandem, these findings indicate greater amount of fatiguing contractions both between groups and between sides. The greater and asymmetrical glucose uptake values were likely due to the leg strength asymmetry in MS.

Asymmetry in bone mineral density (BMD) at the femoral neck was found between the more and less-affected sides, with the more affected paretic limb having a lower BMD.[45] This BMD asymmetry is similar to other reports of unilateral disorders and may be due to irregular loading and muscle weakness.[45]

As discussed above, bilateral differences in oxidative capacity, workload, and overall muscle strength were reported by Larson et al. 2013.[5] The muscular changes in metabolic pathways and strength MS likely played a role in this finding.

Cameron et al. 2008 described asymmetrical postural response latencies (time for afferent or efferent signals) in the legs of people with MS having a range of times from 3-37 milliseconds, where the healthy controls had a range of 0-10 milliseconds ($p=0.005$).[14] The asymmetry is most likely due to the random amount and location of lesions in the spinal cord. The authors speculated that individuals with MS likely rely on the leg with the shorter latency for maintenance of postural stability.

Literature Review Conclusions

In this review we have discussed asymmetries as they pertain to MS. People with MS clearly have issues maintaining balance and show muscle weakness compared to healthy controls. Balance deficits in MS are mainly due to delays in somatosensory afferent feedback and poor central integration of sensory information.[15] However muscle weakness may contribute to fall risk due to reduced inability to correct posture once balance is lost.[99] Asymmetries in weight distribution[13] and strength[6,99] are associated with poor balance. Strength deficits in MS are due to a combination of widespread atrophy from altered muscle physiology and localized regions of poor neuromuscular activation from lesion activity.

Asymmetries in weight distribution during quiet stance[6,78] and strength[5,28] have been documented, albeit in relatively few studies. These asymmetries correlate with measures of functional ability such as balance,[6] walking speed,[5] symptomatic fatigue.[6] In other populations, functional asymmetries relate to poor functional ability.[11,13] Asymmetries in people with MS may affect disability level, daily living, and quality of life.

METHODS

Participants

Thirty-seven people with MS (28 women), recruited through the local neurorehabilitation center, emails, and word of mouth, participated in the study (Table 1). Nearly all participants had the relapse-remitting form of MS, however, 3 were secondary-progressive (the progressive form that follows relapse-remitting), and 3 were unsure of disease subtype. Each participant completed the patient-determined disease steps (PDDS) survey to measure disability level.[51] All testing was completed in the morning to minimize fatigue levels of the participants. This study was approved by the local institutional review board. All subjects provided written informed consent after having the project explained to them.

Inclusion criteria for this investigation were a clinically-recognized diagnosis of multiple sclerosis, age between 21 and 75 years, ability to walk 100 meters without assistance, and ability to provide informed consent. Exclusion criteria included any change in medication, signs of relapse activity, or hospitalization in the past 3 months and presence of any additional neurological disabilities.

Table 1*: *Participant characteristics.

n	Age (yr)	Height (m)	Mass (kg)	PDDS	Disease Duration (yr)
37	54.9 (12.5)	1.68 (0.11)	72.8 (16.4)	2 (0-5)	14.2 (9.1)

All values are mean (SD) except for PDDS, which is median (range).

Quiet Standing

Each participant stood quietly for 1 minute in a relaxed position with arms at their sides, eyes open gazing straight ahead at a blank wall, and with knees extended but not locked. A stance width of 10% of each participant's height was marked with tape and centered on adjacent force platforms (Model 4060-10, Bertec Corp, Columbus, OH, USA). Participants stood with their large

toe on each marker for 2 trials. Prior to beginning each trial, researchers ensured the participant was in a stable standing position. During the minute-long trial timing updates were verbally provided every 10 seconds. In between trials, participants took a short break (~ 90 seconds) to minimize fatigue and mentally reset.

Sit-to-Stand

Participants transferred between sitting and standing five times as safely, but as quickly as possible using methods similar to Moller et al.[10] In short, they started and ended in the seated position and performed the test with arms crossed in front of the chest. After a few seconds of quiet sitting, the test was initiated by the participant's own movement. Feet were at a comfortable width with one foot on each force platform. The seat of the chair measured 44 cm from the ground and lacked arm rests. Prior to the start of the 5xSTS, the researchers ensured that the participant's feet were fully on each force platform and the legs of the chair were not touching the force platforms. Each participant performed the 5xSTS test twice.

Strength Testing

At least one week, and no more than 2 weeks following the quiet stance and sit-to-stand testing, unilateral knee extensor and flexor strength were measured using a customized upright sitting knee extensor resistance training machine. A force transducer (LCHD-250, Omegadyne, Inc. Sanbury, OH, USA) was connected to the swingarm of the machine which was locked in place during the maximum voluntary isometric contractions (MVIC). The padded transducer was strapped anteriorly and slightly above the ankle. With their knee joint set at 90°, participants pushed (knee extensors) or pulled (knee flexors) while sitting with arms across the chest and a seat belt over their lap to prevent excessive body movement. A few non-maximal practice trials were performed before testing to familiarize the participants to the method. Vigorous verbal inspiration

from the researchers was provided while the participants performed MVICs with a duration of 3 seconds until peak forces plateaued within 10% from trial to trial, typically 3-5 trials. Individual knee extensor strength was assessed first, followed by the knee flexors. Starting with the self-reported more/less-affected limb order of testing was alternated between participants.

Sidedness and Asymmetry Calculations

Rather than using solely self-report or raw strength, each participant's more affected (MA) and less affected (LA) sides were distinguished by knee extensor and flexor MVIC along with self-report. The symmetry index[115,116] (SI) for strength was calculated from the sum of knee extensor and knee flexor maximum voluntary contractions where: $SI = \frac{Sum\ Right - Sum\ Left}{0.5(Sum\ Right + Sum\ Left)}\ x\ 100\%$. The stronger limb was determined to be less affected when absolute SI ≥ 10%. If absolute SI < 10%, then the self-reported less affected side was used. Sixteen of the participants had a strength SI < 10%, and self-report disagreed with strength SI in only 6 of those 16.

Asymmetries were also expressed in terms of SI, but were calculated using the LA and MA sides and further categorized as relative (RSI) and absolute (ASI). RSI determines to which side the asymmetry is focused, and is calculated as: $RSI = \frac{LA - MA}{0.5(LA + MA)}\ x\ 100\%$. ASI shows the overall amount of asymmetry present in a population, and is calculated as ASI = |RSI|.

Data Analysis and Statistics

Ground reaction forces and moments were sampled through Nexus (version 1.8.5, Vicon Motion Sytems Inc., Oxford, UK) under each foot at 100 Hz. Individual foot centers of pressure (COPs) were automatically calculated within Nexus. Customized MATLAB (version R2014b, Mathworks, Natick, MA, USA) code was used to low pass filter (recursive, 10 Hz cutoff) and compute parameters for analysis. Individual foot forces and COPs were used to compute the combined (net) COP from which anterior-posterior (AP) and medial-lateral (ML) sway (maximum

minus minimum COP position), path length, and variability (COP standard deviation) over the course of the 1 minute quiet standing trials. All COP distance variables were normalized to standing height (%Height). Ground reaction force variables were normalized to body weight (%Weight). RSI and ASI were then computed for the force variables. Each set of two trials (e.g. the two 5xSTS trials) were averaged together to create a representative value before statistical analysis.

Quiet stance variables included average vGRF RSI & ASI over the entire minute of the trial along with the net COP balance measures of sway, path length, and variability in AP and ML directions. Variables for the 5xSTS included instantaneous maximal vGRF RSI & ASI and average vGRF RSI & ASI. The 5xSTS trial began once the participant's total vGRF reached a threshold of 150% of the initial force (leg weight) on the force platforms. The 5xSTS trial ended once the total vGRF dropped below the threshold for the 5^{th} time.

Statistical procedures were calculated in SPSS (version 23, IBM Inc., Chicago, IL, USA). All first-tier outliers (extreme values outside of the interquartile range (IQR) by ≥ 3 x IQR) were removed. Second-tier outliers (values outside of the IQR by ≥ 1.5 x IQR) were removed one at a time until data was found to be normal in terms of skewness and kurtosis.[119] Repeated measures ANOVA was used to identify any differences in RSI or ASI levels between the 5 variables: quiet stance average vGRF, 5xSTS average vGRF, 5xSTS peak vGRF, knee extensor force, and knee flexor force. Bonferroni post hoc comparisons were used to analyze any significant main effects of the ANOVA. Pearson correlations were used to identify associations between characteristic, postural stability, 5xSTS, and strength variables. Statistical significance was set to $\alpha = 0.05$. Unless otherwise noted, data are presented as *mean (SD)* while r signifies Pearson Correlation value.

Outliers Removed from Dataset

All variables were found to be normal without having to remove non-outlier values. There were typically few outliers, and the most any variable had removed to make normal was three subjects. In the quiet stance dataset, 2 first-tier and 1 second-tier outlier were removed for ML sway. In AP sway, 1 first-tier outlier was removed. For ML path length, 2 first-tier outliers were removed. In AP path length, 1 first-tier outlier was removed. For ML variability, 2 first-tier outliers were removed. There were no outliers for the 5xSTS dataset. For the strength dataset, 1 first-tier outlier was removed for knee extensor ASI. For knee flexor RSI, 1 first-tier outlier and 2 second-tier outliers were removed. In knee flexor ASI, 1 first-tier and 1 second-tier outlier was removed.

RESULTS

Balance characteristics during quiet stance are presented in Table 2. MVIC Strength values for the group are presented in Table 3.

Asymmetry Levels between Tests

The RSI repeated measures ANOVA revealed significant differences between tests (P = 0.010) (Figure 7). Post-hoc comparisons showed that knee extensor strength RSI was greater and favored the less-affected side compared to 5xSTS average vGRF RSI and 5xSTS peak vGRF RSI. No other mean differences were found for RSI. Repeated measures ANOVA for ASI yielded differences in the same variables as RSI (P = 0.010) (Figure 8).

Table 2: *Net balance characteristics for the group.*

ML			AP		
Sway	**Path Length**	**Variability**	**Sway**	**Path Length**	**Variability**
78 (30)	2010 (545)	16 (7)	175 (51)	3803 (1121)	33 (12)

ML = Medial-Lateral, AP = Anterior-Posterior. All values are mean (SD) and all units are %Height.

Table 3: *Unilateral strength characteristics for the group.*

Less-Affected		More-Affected	
KE Strength	**KF Strength**	**KE Strength**	**KF Strength**
54.1 (17.8)	22.3 (9.7)	48.1 (18.3)	19.0 (9.3)

All values are mean (SD). Units for all values are %BodyWeight.

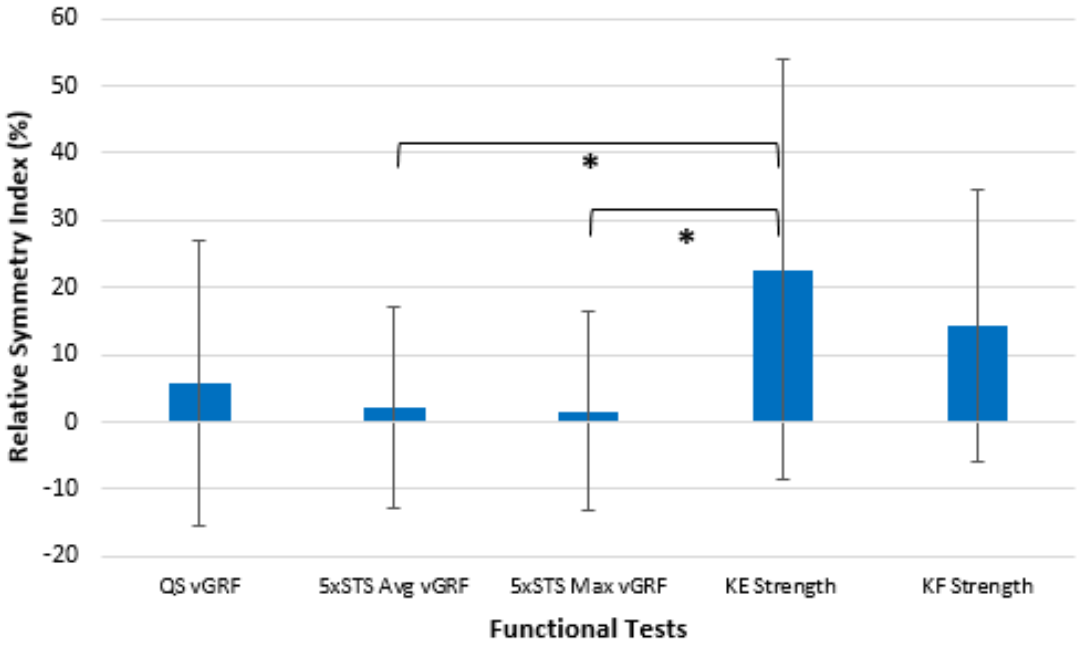

Figure 7: *Relative Symmetry Index (RSI) for each of the functional tests in this study. A positive RSI signifies higher levels on the less-affected side while negative values would represent greater values on the more-affected side. An asterisk (*) indicates P ≤ 0.05.*

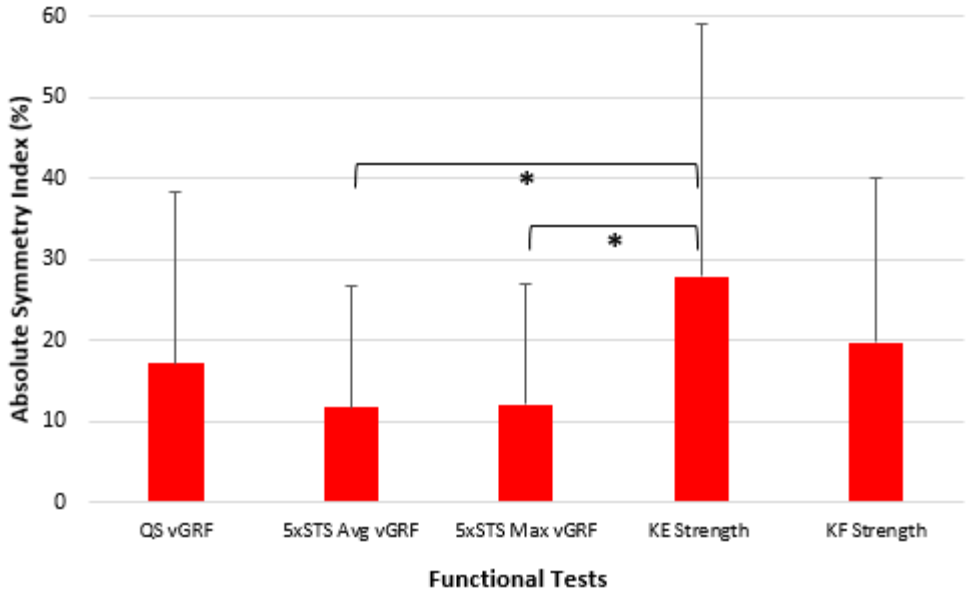

Figure 8: *Absolute Symmetry Index (ASI) for each of the functional tests. An asterisk (*) indicates P ≤ 0.05.*

Significant Correlations Involving Asymmetry Levels

The only asymmetry levels that were significantly correlated between the various tests were quiet stance ASI with 5xSTS average ASI (r = 0.341, *P* = 0.039) and 5xSTS max ASI (r =

0.359, *P* = 0.029). Asymmetry levels significantly correlated to other measures in the study as well. Quiet stance vGRF ASI correlated with balance characteristics of AP path length (r=0.457, *P* = 0.005) and ML variability (r = 0.409, *P* = 0.015). Mean 5xSTS ASI correlated with PDDS (r = 0.462, *P* = 0.004), ML sway (r = 0.397, *P* = 0.020), and AP path length (r = 0.372, *P* = 0.026). All correlations involving asymmetry levels are shown in Table 4 and a diagram of associations can be seen in Figure 9.

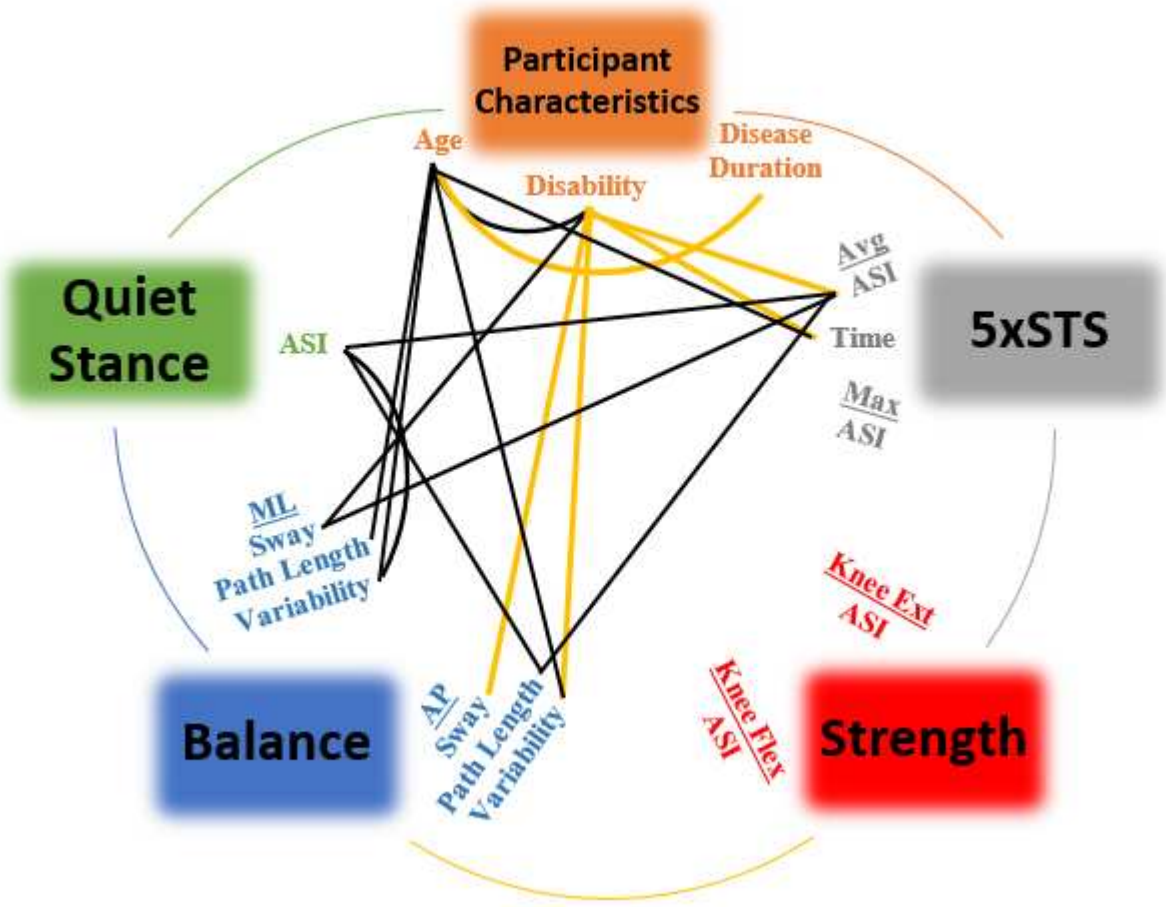

Figure 9: *Spider web diagram of all significantly correlated variables. As seen above, the most correlated asymmetry variables were those involving the 5xSTS. Table format of the above correlations can be found in greater detail in Table 4.* ***Black*** *lines signify P ≤ 0.05, and yellow lines signify P ≤ 0.01.*

Other Significant Correlations

Other significant correlations levels were found between PDDS and age (r = 0.342, *P* = 0.038), ML sway (r = 0.424, *P* = 0.013), AP sway (r = 0.450, *P* = 0.006), AP variability (r = 0.479,

P = 0.003), and 5xSTS time (r = 0.542, *P* = 0.001). Age correlated with disease duration (r = 0.493, *P* = 0.002), ML path length (r = 0.340, *P* = 0.046), ML variability (r = 0.388, *P* = 0.021), AP variability (r = 0.337, *P* = 0.041), and 5xSTS time (r = 0.378, *P* = 0.021). AP variability correlated with 5xSTS time (r = 0.347, *P* = 0.036). Additionally most of the balance characteristics correlated with each other (Figure 9).

Table 4: *List of correlations of asymmetry levels (ASI) and other variables. For each correlation, the top row is the r value and the bottom, shaded row is the P value. PDDS = Patient Determined Disease Steps (indicator of disability level), vGRF = vertical ground reaction force, QS = quiet stance, ML = medial-lateral, AP = anterior-posterior, 5xSTS = five times sit-to-stand, KE = knee extension, KF = knee flexion. Category colors follow those seen in Figure 3. An asterisk (*) indicates that P ≤ 0.05, and a double asterisk (**) indicates that P ≤ 0.01.*

	PDDS	Age	Disease Duration	QS vGRF ASI	ML Sway	AP Sway	ML Path Length	AP Path Length	ML Variability	AP Variability	5xSTS Time	Avg vGRF ASI	Max vGRF ASI	KE ASI	KF ASI
QS vGRF ASI	0.181	0.133	0.144	r	0.334	0.300	0.123	0.457**	0.409*	0.126	0.105	0.341	0.359	0.086	-0.104
	0.284	*0.433*	*0.396*	*P*	*0.054*	*0.076*	*0.482*	*0.005*	*0.015*	*0.456*	*0.537*	*0.039*	*0.029*	*0.619*	*0.552*
5xSTS Time	0.542**	0.378*	0.143	0.105	0.294	0.310	-0.167	0.177	0.217	0.347*	r				
	0.001	*0.021*	*0.398*	*0.537*	*0.091*	*0.066*	*0.338*	*0.301*	*0.210*	*0.036*	*P*				
Avg vGRF ASI	0.462**	0.204	0.113	0.341*	0.397*	0.188	0.139	0.372*	0.323	0.110	0.256	r			
	0.004	*0.226*	*0.506*	*0.039*	*0.020*	*0.271*	*0.425*	*0.026*	*0.059*	*0.516*	*0.127*	*P*			
Max vGRF ASI	0.131	0.095	0.150	0.359*	0.175	0.075	-0.180	0.020	0.186	-0.011	0.133	0.583**	r		
	0.441	*0.577*	*0.377*	*0.029*	*0.323*	*0.662*	*0.301*	*0.908*	*0.284*	*0.948*	*0.434*	*0.000*	*P*		
KE ASI	0.200	0.029	-0.247	0.086	-0.128	-0.316	-0.209	-0.184	-0.113	-0.284	0.081	0.070	-0.090	r	
	0.243	*0.866*	*0.147*	*0.619*	*0.477*	*0.065*	*0.235*	*0.289*	*0.526*	*0.093*	*0.641*	*0.684*	*0.603*	*P*	
KF ASI	0.159	0.268	0.081	-0.104	0.131	-0.211	0.270	0.193	0.114	-0.255	0.037	0.282	0.007	0.225	r
	0.361	*0.119*	*0.642*	*0.552*	*0.474*	*0.230*	*0.129*	*0.275*	*0.528*	*0.139*	*0.831*	*0.101*	*0.969*	*0.193*	*P*

DISCUSSION

In this study, we sought to examine levels of asymmetries during quiet stance, 5xSTS task, and knee joint strength and how they associate with each other as well as with balance, physical function, and disability level. We reject our 1st hypothesis that weight distribution and strength asymmetries would be similar in magnitude between the tests. There was a wide range of asymmetry levels in both RSI and ASI even though only a few were statistically different across the tests. We partially accept the 2nd hypothesis that these asymmetries levels would be correlated to each other. We found that weight distribution asymmetries were significantly associated between quiet stance and 5xSTS, but correlations were relatively low and strength asymmetries were not significantly correlated to any other variable. We accept the 3rd hypothesis that asymmetries would be significantly associated with 5xSTS measures of physical function and disability. Quiet stance asymmetries associated to balance ability whereas 5xSTS asymmetries correlated to balance and disability level. Again, however, correlations were low to moderate ($r < 0.600$).

Asymmetry Levels in MS

Unilateral dysfunction in the MS population has been described in many forms. To date, asymmetries in people with MS have been reported in strength[5], power[5–7], weight distribution while standing[6,78], oxygen uptake[5,8], glucose uptake[28], and bone mineral density.[45] No study to our knowledge has reported weight distribution asymmetries during a 5xSTS in people with MS. Because the 5xSTS is largely dependent upon lower body strength[10], we found it surprising that asymmetry levels during the 5xSTS were not closer to the levels of strength asymmetries. It seems that even though there is a large discrepancy in bilateral strength, when accomplishing a functional symmetrical task such as the 5xSTS, there is a more uniform weight distribution between sides.

One reason for this may be that the participants were using both sides simultaneously for the 5xSTScompared to only one side at a time for the strength testing. Another reason for this difference is that maintaining balance is required for the 5xSTS. If there were a large asymmetry in leg force production, balance may be lost during the task. A third reason why there was no difference between strength and 5xSTS tests is that strength was a maximal effort task while the 5xSTS was sub-maximal. If performed at the same intensity, they may have been more similar.

Bowser et al. found differences between legs in max knee extensor power during a single sit-to-stand task, but did not report weight bearing asymmetries during the task.[7] Similar results in joint moment asymmetries during the sit-to-stand task have been found in hemi-paretic stroke patients[18] and healthy individuals.[120] Outside of MS, Christiansen et al. found that weight bearing asymmetries and ratios in patients recovering from total knee replacement had greater differences than healthy controls and the asymmetries were associated with quadriceps strength and functional mobility.[11] However, the authors did not report significance values of these correlations, making it difficult to determine exactly how the weight-bearing ratio may affect strength and mobility. Houck et al. 2011 documented sit-to-stand asymmetries in people following a hip fracture, and the bilateral differences correlated with gait speed and self-reported functional mobility.[121]

Strength and power asymmetries are the most documented type of asymmetries in people with MS. We found large amounts of asymmetry in isometric strength (ASI = 27.9 (17.7) and 19.8 (17.4) % for the knee extensors and knee flexors respectively) with the less-affected limb being stronger, mostly agreeing with strength asymmetries in previous studies. Chung et al. documented knee extensor power asymmetry score of 21.5 (16.2)% MS vs 9.2 (6.9)% control, $P = 0.02$, no statistical bilateral differences were found for isometric strength.[6] Larson et al. found strength and power bilateral differences in their population of people with MS, however instead of calculating

an asymmetry level they reported bilateral differences.[5] Lambert et al. described lower amounts of knee extensor and flexor dynamic torque in people with MS compared to healthy controls, and found varying bilateral strength measures of knee extension and flexion in the MS group, however it was non-significant.[9] Rudroff et al. documented asymmetries in isometric knee flexion strength and in glucose uptake of the legs following 15 minutes of walking.[28] They speculated that asymmetries in muscle strength along with oxygen consumption[5,8] and glucose uptake asymmetries may limit functional abilities in people with MS. Differences in asymmetry calculations and methodology (isometric vs dynamic strength) may explain the differences between the present study and previous studies.

Weight distribution asymmetry levels during quiet stance did not differ from asymmetries during the 5xSTS and in strength. With a greater sample size, these differences may become significant. On average, quiet stance weight distribution RSI and ASI was in between the other two tests, higher than 5xSTS, but lower than strength. The lack of differences between quiet stance asymmetries and the other tests may be due to the task's reliance on balance ability and simplicity. In our study and others[6,13] weight distribution asymmetries are related to balance ability. When people with MS try to minimize movements during a balance test, they may adopt symmetrical stance. This may explain why quiet stance asymmetries were slightly lower than strength asymmetries on average. The simplicity of the quiet stance test may allow for a higher level of weight distribution asymmetries while still being able to complete the task. This may explain why the quiet stance asymmetries were slightly higher than the 5xSTS on average. We are unsure if a greater level of weight distribution asymmetries would be present in normal stance, when they are not actively trying to stand as still as possible, thereby minimizing COM movement.

Chung et al. documented a significant difference in weight bearing asymmetry score of between people with MS and healthy controls during quiet standing (10.5 (6.9) vs 6.0 (3.0) %, $P = 0.05$).[6] Van Emmerik et al. documented a similar weight distribution asymmetry score and also looked at weight distribution asymmetries during a leaning and reaching task, finding that greater weight distribution asymmetries during backwards leaning.[78] Our quiet stance vGRF ASI of 17.1 (13.6) % is greater than weight distribution asymmetries found by Chung et al. and Van Emmerik et al. Other groups have documented weight distribution asymmetries during quiet stance in other populations than MS with similar results. Blaszczyk et al. 2000 found greater limb loading asymmetries in the elderly compared to a young group.[13]

Associations between Asymmetry Levels

Due to the necessity for muscle strength during the sit-to-stand task and weight distribution task similarities between quiet stance and the 5xSTS we expected to find associations in asymmetry levels between the tests. Neither measure of muscle strength significantly related to the average or maximum instantaneous vGRF asymmetry level during the 5xSTS. This agrees with Chung et al., who did not find significant correlations between weight distribution asymmetries and knee extension power asymmetries.[6] Asymmetry levels during the two weight distribution tasks were significantly correlated. No study to our knowledge has reported correlations in weight distribution asymmetry between quiet stance and the 5xSTS.

Associations between Asymmetries and Physical Function

Functional asymmetries may contribute to physical function or disability, perhaps due to the performance of symmetrical activities for daily life (walking, standing, and sitting) or by potentially increasing muscular fatigue due to chronic compensation of these asymmetries.[28] In this study, we found that average 5xSTS weight distribution asymmetries correlated with disability

level and aspects of balance ability. Asymmetries in weight distribution during quiet stance correlated to balance ability as well.

MS has unfavorable effects on balance ability.[15] Poor balance measures correlate with higher levels of disability.[68] Interestingly, even though the 5xSTS asymmetries had the lowest levels on average, they significantly correlated with the balance and disability more than the other tests. For these reasons, we believe that the 5xSTS would be the most reliable functional assessment in people with MS, of those we examined, especially when measuring weight distribution asymmetries. However, considering the relatively low level of the correlations ($r < 0.600$), predictability from this measure is lacking.

Many studies (in MS and other categories) have documented significant associations between balance and strength. Strength in nearly all the major muscles of the lower limb is associated with poor postural stability in individuals with MS.[92] Chung et al. reported balance measures of AP COP variability correlating with knee power asymmetry and loading asymmetry, and ML COP variability correlating with loading asymmetry.[6] In this study, we did not find any significant correlation between asymmetries in isometric strength and balance ability, thus asymmetries in static strength are likely not related to postural stability in people with MS. Balance ability was associated with weight bearing asymmetries during the 5xSTS and quiet stance trials. Blaszczyk et al. found similar results in an elderly population where limb loading asymmetries during quiet stance associated with increased postural sway.[13] The authors speculated that unloading one limb may allow for a quicker step response to regain balance.[13] It is unknown if the limb loading asymmetry seen in the MS population is for the same reason.

Isometric strength asymmetries did not significantly correlate to balance, weight distribution asymmetries, or disability in people with MS. Larson et al. found that bilateral

differences associated with functional performance in the 6 minute walk test.[5] As reported above, Chung et al. documented an association between knee power asymmetry and AP variability. A potential reason for why we did not find associations between strength asymmetry and other indicators of functional ability is that we did not assess dynamic strength, instead measuring strength isometrically. Chung and Larson both used a dynamic strength testing protocol which may be more sensitive to functional strength compared to isometric measures.

In addition to the weight distribution asymmetry correlations above, Chung et al. found that quiet standing weight distribution associated to symptomatic fatigue in the fatigue severity scale. Although fatigue was not measured in this study, asymmetries may have an effect on fatigue. Rudroff et al. concluded that strength asymmetries along with metabolic asymmetries in muscle tissue during activity may contribute to muscle fatigue and impairments in daily activities such as the sit-to-stand task or walking.

Limitations

As with any investigation, our study has its limitations. First, is that we did not compare asymmetry levels between people with MS and healthy controls. Various studies have documented functional asymmetries in the MS population in the past.[5,6,78] Although our group may have greater levels of asymmetry compared to a healthy population, we cannot support this claim in this investigation.

Another limitation is repeatability. Although we did have the participants perform two trials of each test and used the average for comparison, there may be day-to-day variability in asymmetry levels and we did not address this. Variability levels in asymmetry levels have not been investigated in people with MS. It is possible that asymmetries in functional tasks can vary day-to-day in this population.

A third limitation is that we used a different symmetry calculation than others. Differences in asymmetry levels between this study and the others may be due to the asymmetry calculations. Multiple symmetry equations have been used in the bilateral symmetry literature, making it difficult to compare asymmetry levels between studies. These differ by which group is performing the tests and what parameters are being assessed. In this study we used symmetry index[115,116] to calculate bilateral asymmetries. Chung et al. used one equation for strength asymmetry and an entirely different equation for limb loading asymmetry, which was also used by Van Emmerik et al.[6,78] Larson et al., and Bowser et al. to simply determine whether asymmetries were present.[5,7] In a non-MS population, Christiansen et al. simply used a ratio to quantify 5xSTS asymmetry levels among patients recovering from total knee arthroplasty.[11,17]

One more limitation is that we did not measure knee extensor or flexor power or other functional tasks such as walking. Two of the previous studies found bilateral asymmetries in muscle power.[5,6] Another study found functional asymmetries in workload during the sit-to-stand task.[7] It is possible that dynamic strength measures associate to functional ability more than static strength measures, especially since the other studies found associations between muscle power and balance. Additionally, this study would be more relatable to others if we were able to add gait asymmetries to the other tests and identify any correlations in asymmetries to strength and weight distribution during the 5xSTS and quiet stance.

CONCLUSIONS

Knee extensor strength asymmetries are greater than weight distribution asymmetries during the 5xSTS in people with MS. Asymmetry levels in knee flexor strength and weight distribution during quiet stance are not different from the other tests mentioned above. Although the 5xSTS weight distribution asymmetries have the lowest levels, they are significantly correlated to weight distribution asymmetry during quiet stance, balance, and disability level in our MS population. Isometric strength asymmetries were not associated to any other functional asymmetries or measures of functional activity, thus they should not be used as an indicator of functional ability. Clinical assessments of asymmetry in one task may not carry over to other tasks. Further research on sit-to-stand asymmetries, other strength asymmetry tests, and measures of physical function is needed to determine how asymmetries affect daily activities and quality of live in people with MS.

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