Accelerometry Coherence Analysis To Assess Balance Strategies In Patients With Multiple Sclerosis

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List of Abbreviations

Abbreviation	Full Term
CNS	Central Nervous System
MS	Multiple Sclerosis
Mod	Moderate
Ctrl	Control
QS	Quiet Standing
MRI	Magnetic Resonance Imaging
WHO	World Health Organization
EDSS	Expanded Disability Status Scale
FSS	Function System Score
ABC	Activities-specific Balance Confidence
MSWS-12	Multiple Sclerosis Walking Scale-12
MAS	Modified Ashworth Scale
BoS	Base of Support
EMG	Electromyography
CSF	Cerebral-Spinal Fluid
CoM	Center of Mass
CoP	Center of Pressure
SEPP	Somatosensory Evoked Potentials

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Abstract

Patients with multiple sclerosis often complain about reduced balance and have increased sway during quiet standing. However, thus far, no investigations have been conducted to identify the altered balance strategies used by these subjects while standing upright. Recently, young healthy adults were found to use an inverted pendulum-like, ankle strategy during quiet standing below 1Hz and a double inverted pendulum-like hip strategy above 1Hz. Here we present evidence for a difference in balance strategies used by subjects with MS compared to control subjects, using coherence and cophase analysis of trunk and leg segment accelerometry and kinematics. A high coherence together with a low cophase relationship was defined as ankle strategy, whereas a high coherence together with a 180 degrees cophase was defined as hip strategy. Thirty-seven subjects with MS and 20 healthy age-matched control subjects stood quietly for 30 seconds for 3 trials in each of two conditions: eyes open and eyes closed. Balance strategies were determined by calculating coherence and cophase at particular frequency intervals using a kinematic gold standard of trunk and shank angles in space compared with a novel use of accelerometry. Severity of MS was classified three ways: anterior-posterior sway range, delays of postural response latencies to surface translations, and walking speed. Neither latency nor walking speed was able to differentiate balance strategies between mild MS, moderate MS, and controls. Several methods were evaluated for quantifying a change in balance strategy, including the frequency at which the cophase crosses 90° and the frequency of the coherence minimum. Neither method using specific, single metrics showed significant difference among groups. The best method of distinguishing balance strategies among groups involved comparing group differences in coherence and cophase trends across all frequencies. Subjects classified as moderate based on postural sway range were found to have significantly lower coherence at the low frequencies coupled with a near zero cophase, suggesting a reduced or uncoordinated use of ankle strategy compared to control subjects or subjects with mild MS. However, postural response latency and gait speed only moderately predicted balance strategies in subjects with MS. Accelerometry measures yielded similar results to kinematics in coherence, but not cophase, analysis

across frequencies supporting the potential validity of accelerometers in measuring balance strategies during quiet stance. Accelerometry approach to measuring balance strategies, however, may be limited by the coupling of tangential and gravitational accelerations during body sway.

Chapter 1 Introduction

Section I - *Multiple Sclerosis*

Multiple sclerosis (MS) was first clinically and pathologically described by Jean-Martin Charcot and Edme Vulpian in 1866 [1] as a disease distinguished by the scattered plaques in the brain and spinal cord. Although nearly a century and half has passed since its initial description, the etiology and distinct diagnostic biomarkers of multiple sclerosis have remained elusive. Currently, MS is often referred to as a progressive, autoimmune and inflammatory disease affecting the white matter of the central nervous system that leads to the demyelination of CNS neurons.

Although much is understood about the mechanisms involved in the disease process, the underlying cause is still unknown. CNS inflammation is the primary cause of nervous system damage in MS, but the exact factors that initiate this inflammation have yet to be discovered. However, it is believed that environmental factors in genetically susceptible individuals trigger a T-cell autoimmune response against the CNS.[2] Recent studies have begun to identify genes that are associated with MS such as the major histocompatibility complex which affects both the immune repertoire and immunoregulatory circuits along with the DRB*1501 allele which is linked to disease severity.[3] Other research has implicated not only T cell reactivity but also focal changes in the blood brain barrier permeability and defective immune regulation.[4]

Furthermore, the distinct types and stages of multiple sclerosis are now being attributed to different components of the immune system, namely the innate and the adaptive.[5] Neurodegeneration can be directly caused by immune cells such as cytotoxic CD8 cells, damaging neurons or macrophages stripping myelin from the axon, or as a result of the release of toxic intermediates such as glutamate or nitric oxides which can trigger immune cascades that further enhance inflammatory-mediated CNS damage.[6]

White matter is given its visual characteristics by myelin, an insulating material that coats the majority of axons in the central nervous system, allowing for faster conduction of electrical signals to and from the brain.[7] In the CNS, oligodendrocytes extend and wrap their membranous processes around many axons, creating many layers of insulation called the myelin sheath. In the peripheral nervous system (PNS), Schwann cells encompass a single axon in a similar fashion to oligodendrocytes in the CNS. Figure 1A shows the progression of myelination of an axon in the PNS by a Schwann cell, beginning with only one wrapping, and considered fully sheathed with the presence of a large number of wrappings. The thickness of the insulation material decreases the axon's conductivity, which ultimately increases action potential propagation. Every 1-2mm along the axon are nodes of Ranvier which are small segments containing no myelin sheath but a very high density of ion channels.[8] These nodes allow for propagation of the electrical signals within neurons, in essence boosting the signal as it travels from the soma to the axon terminal. The combination of myelin sheath and nodes of Ranvier causes the action potential to move by salutatory conduction as demonstrated in figure 1C by the red arrows depicting an action potential bypassing

sheathed sections .[7] Furthermore, this figure illustrates the high flow of ions at nodes or Ranvier, maintaining the depolarization of the signal as it travels along the axon.

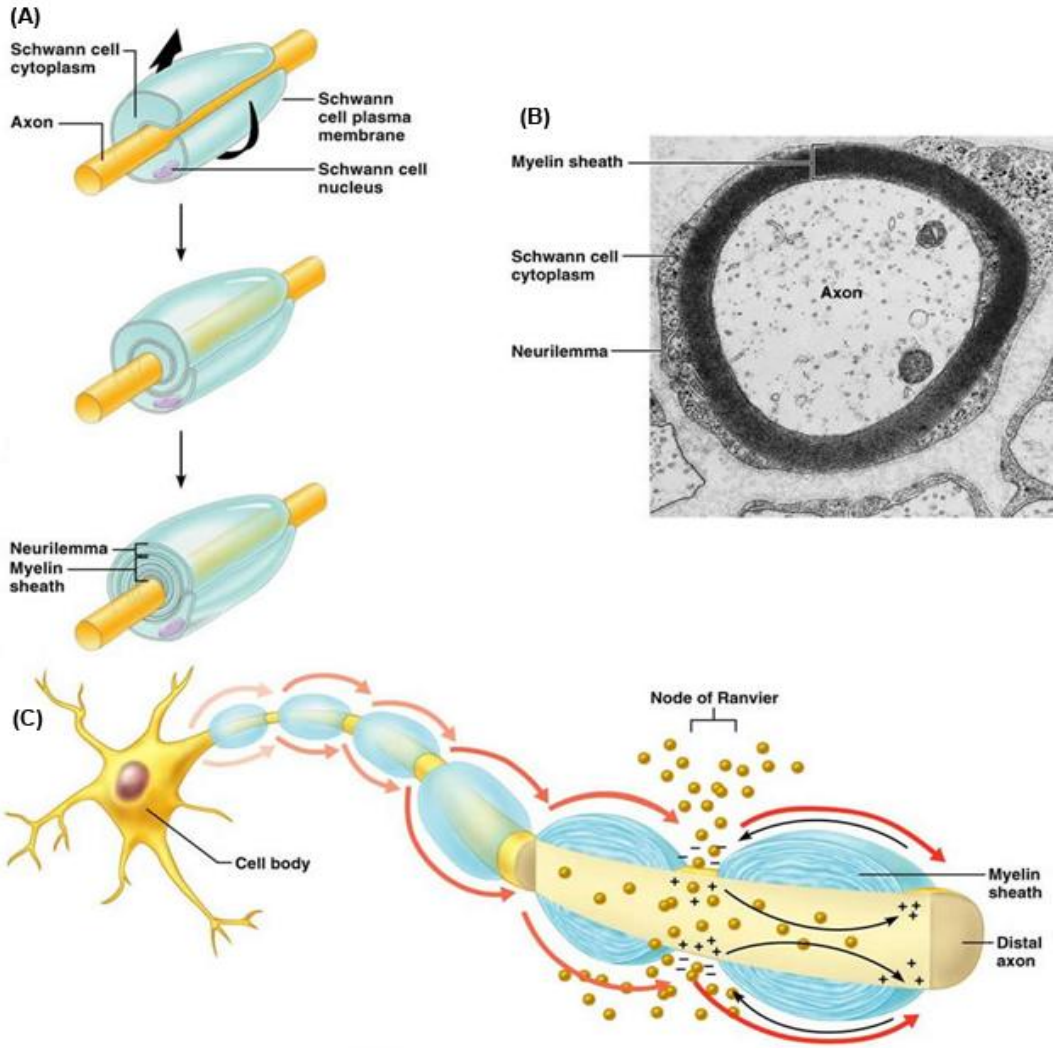

Figure 1. An overview of myelin and myelination. (A) Progression of myelination of an axon by a Schwann cell during development in the PNS. Early stages of myelination involve the envelopment of the axon by the Schwann cell cytoplasm. A fully myelinated axon possesses many layers creating what is termed the myelin sheath. (B) An electron micrograph crass section of an axon with its surrounding sheath. (C) A representation of a neuron, depicting salutatory conduction as well as ion influx and efflux at a node of Ranvier. Adapted from Marieb and Hoehn, 2006.[7]

The name *multiple sclerosis* refers to the scleroses, or scars (also known as plaque or lesions) found scattered throughout the CNS. The presence of these lesions leads to

demyelination and accompanying neurological symptoms. Recent MRI studies have found that lesions are not only found in the white matter (superficial areas of the brain) but also in the grey matter, under the cortex. These findings could explain the appearance of cortical lesions without any marked change in clinical appearance as well as the onset of new symptoms without new superficial lesions. Other MRI and pathological studies have shown that gray matter atrophy is linked to cognitive impairment.[9]

The disease manifests itself clinically in many different ways, affecting the motor, sensory, visual, and autonomic systems and is the most common neurological disease affecting young adults.[10] Common symptoms include focal muscle weakness, visual disturbances, bowel dysfunction, fatigue, cognitive changes, and sensory impairments.[10] Table 1 on the following page shows a more extensive list of many common signs and symptoms of MS, organized by the site of affliction.

	Symptoms	Signs
Cerebrum	Cognitive impairment	Deficits in attention, reasoning, and executive function (early); dementia (late)
	Hemisensory and motor	Upper motor neuron signs
	Affective (mainly depression)	
	Epilepsy (rare)	
	Focal cortical deficits (rare)	
Optic nerve	Unilateral painful loss of vision	Scotoma, reduced visual acuity, colour vision, and relative afferent pupillary defect
Cerebellum and cerebellar pathways	Tremor	Postural and action tremor, dysarthria
	Clumsiness and poor balance	Limb incoordination and gait ataxia
Brainstem	Diplopia, oscillopsia	Nystagmus, internuclear and other complex ophthalmoplegias
	Vertigo	
	Impaired swallowing	Dysarthria
	Impaired speech and emotional lability	Pseudobulbar palsy
	Paroxysmal symptoms	
Spinal cord	Weakness	Upper motor neuron signs
	Stiffness and painful spasms	Spasticity
	Bladder dysfunction	
	Erectile impotence	
	Constipation	
Other	Pain	
	Fatigue	
	Temperature sensitivity and exercise intolerance	

TENS=transcutaneous electrical nerve stimulation.

Table 1. Signs and symptoms of multiple sclerosis, organized by site. Adapted from Compston and Coles, 2008.[11]

This slowing of neural conduction in the nervous system, especially in the spinal cord, brainstem, sensorimotor cortex, and cerebellum, leads to balance and gait problems in patients with MS. The reduced or lost ability to walk is often the primary concern and complaint that patients have. Recent research has demonstrated that balance and gait problems could be directly influenced by slowed somatosensory conduction velocities of neurons from the legs to the brain.[11] A better understanding of how MS affects

coordination of the upper and lower body for balance control may provide a noninvasive method for measuring severity of involvement of neural pathways important for balance and gait. It will also assist the understanding of the contribution of somatosensory conduction velocity for balance coordination.

1. Epidemiology

The National MS Society estimates that 400,000 people are currently living with MS in the United States, with 200 more being diagnosed every week.[12] A recent World Health Organization (WHO) survey from 2007, including 1.3 million participants from 100 different countries has estimated the prevalence of worldwide MS to be 30 per 100,000, with occurrences as high as 80 and 135 per 100,000 in Europe and America respectively.[13] This suggests that over 2.7 million people worldwide are living with Multiple Sclerosis.

Some epidemiological studies involving geographic, demographic, and migration patterns have implicated environmental factors as a potential cause for MS.[12] Some scientists think the reason may be linked to vitamin D, [14] while others believe genetic factors play a significant role.

The occurrence of multiple sclerosis often begins in early adulthood as most patients are diagnosed between the ages of 20 and 50.[15] The disease is not contagious and has been observed to be more prevalent among Caucasians.

2. Clinical Courses

Multiple sclerosis is most often divided into four disease courses, each of which can further be classified as mild, moderate, or severe: Relapse-remitting, primary progressive, secondary progressive, and progressive-relapsing. These four courses are determined based on the presenting symptoms and temporal evolution of the clinical findings. Although these categories have been defined scientifically, because of the disease's variable nature, the clinical course in an individual is largely unpredictable, sometimes making distinct classification difficult in practice. Despite the variety of clinical courses, in all cases, symptoms evolve over several decades, leading to a median time to death of around 30 years from disease onset, a reduction in life expectancy of 5-10 years.[16] Figure 2 below contains plots of disability over time and short descriptions of the four common manifestations of disease progression in MS.

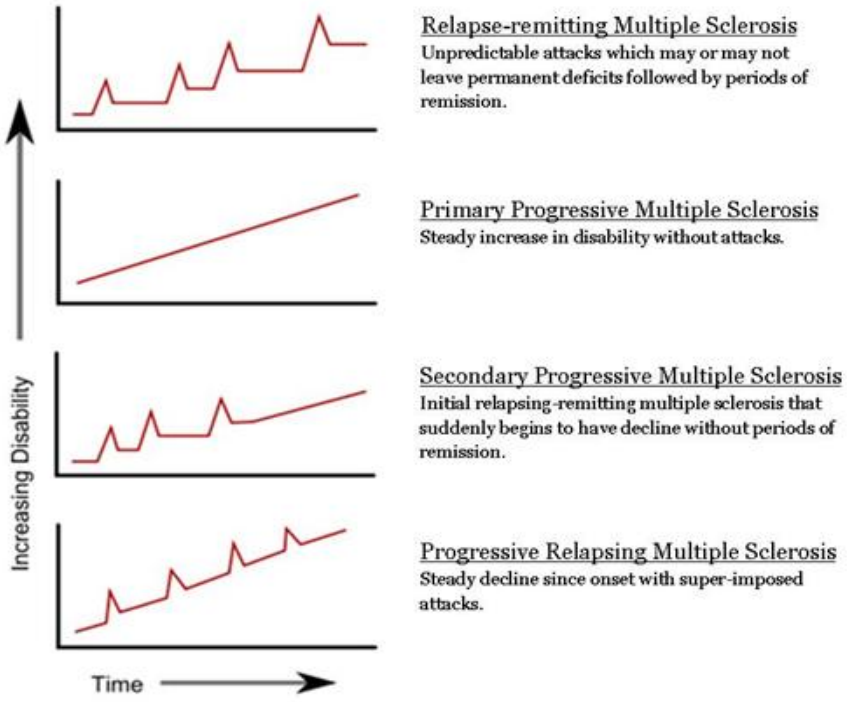

Figure 2. The four common disease manifestations of MS over time. In each form of MS, disability is non-existent but becomes worse over time. Spiking represents a clinical episode or attack which is characterized by a sudden and often temporary increase in disability. Adapted from Wikipedia.[17]

Relapse-Remitting

This form of multiple sclerosis is the most prevalent, consisting of as many as 80 percent of patients, often affecting patients in their 20s and 30s.[12] Furthermore, a female predominance has been approximated at a 2:1 ratio in comparison to their male counterparts.[18] Relapse-remitting patients present with signs and symptoms that evolve and worsen over the course of a few days but eventually the patient recovers fully or nearly fully, with some minor residual deficits. These relapse episodes are characterized by acute worsening of neurological function, followed by long periods of disease stability, known as remissions. New episodes are erratic and seldom exceed 1.5

per year [19] and can be significantly reduced by prescribed medication to one third of their normal occurrence.

Progressive Primary

This disease course is the second most common form of multiple sclerosis, consisting of 10 percent of patients, with a similar incidence among men and women.[18] It is distinguished by the gradual progression of the clinical course. Some patients may have relatively steady worsening of their disabilities over time while others can display occasional plateaus or even brief minor improvements. In order to incorporate both scenarios, it is commonly agreed upon that primary-progressive is determined based on the slowly evolving disease course, over the span of months, which may include minor fluctuations, but no distinct relapses.[20]

Secondary Progressive

Approximately 65% of relapse-remitting patients eventually enter this phase.[19] Secondary progressive is defined as initially following a relapse-remitting clinical course in the early stages followed by a steady progression similar to that of primary progressive MS, with or without minor relapses or plateaus.

Relapsing Progressive

This rare form of multiple sclerosis is attributed to 5 percent of the MS population. These patients present with steadily worsening disease from the beginning but are also

subject to attacks with no remission period. People may or may not have full recovery from relapses, but the disease progresses nonetheless.

3. Diagnosis

Diagnostic criteria have gone through several revisions over the past 50 years, each centered on the dissemination of the disease in time and space. Initially the Schumacher Criteria were used in 1965, which consisted of:

- Neurological examination which reveals objective abnormalities of central nervous system (CNS) function.
- History which indicates involvement of two or more parts of CNS.
- CNS disease which predominately reflects white matter involvement.
- Involvement of CNS which follows one of two patterns:
    - Two or more episodes, each lasting at least 24 hours and at least one month apart.
    - Slow or stepwise progression of signs and symptoms over at least 6 months.
- Patient aged 10 to 50 years old at onset.
- Signs and symptoms which cannot be better explained by other disease process.

These criteria were then modified and elaborated upon by the Poser Criteria. In 2001 an international panel headed by Dr. W. McDonald produced the McDonald Criteria which included the use of magnetic resonance imaging to provide evidence of spatiotemporal dissemination.[21] Further revisions have been introduced in 2005 and 2010, accepting more modern tests and refinements, such as MRIs, but still rely on the demonstration of objective CNS white matter lesions separated in time and space.[22] Cerebral Spinal Fluid (CSF) analysis is also accepted to help establish a diagnosis of MS when there are few other clinical or radiological findings. However, the lack of abnormal spinal fluid is not sufficient for a negative diagnosis.[23] The usefulness of the new McDonald Criteria was evaluated when it was first introduced by comparing clinical definition of MS in 139 patients with a single demyelinating episode. More than three times the patients were diagnosed with MS using the new criteria compared to the old, with a sensitivity of 74%, specificity of 86%, and accuracy of 80%.[24] Figure 3 below is a simplified diagram illustrating the requirements for a diagnosis of multiple sclerosis, in which each row represents a different case.

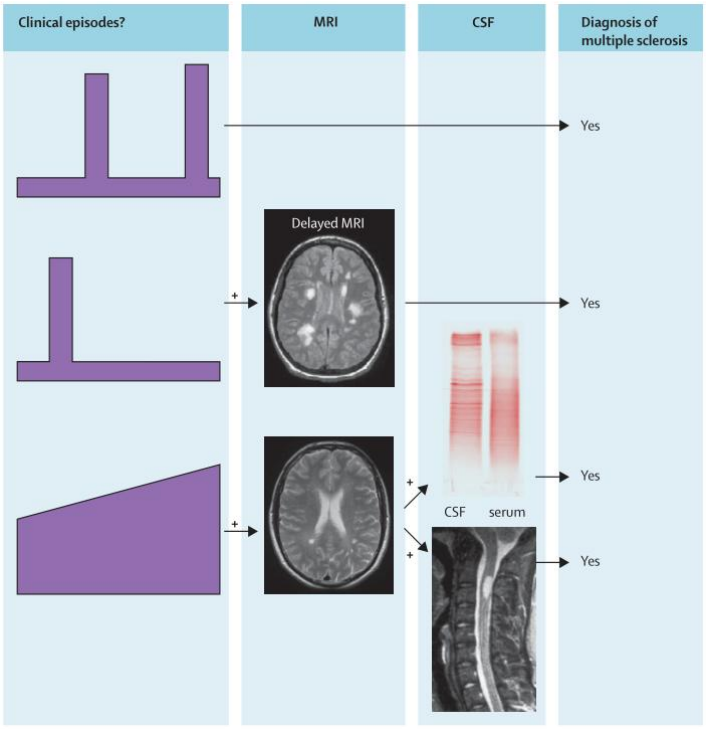

Figure 3. A simplified schematic of the diagnosis of MS. A patient diagnosed with two or more episodes is considered to have MS, as exemplified by the first row. Alternatively, a patient with only one episode accompanied by a lesion containing MRI obtained at a later date is diagnosed, shown in row two. A patient presenting with progressive disability requires an MRI consisting of lesions along with either a CSF test or spinal MRI. Adapted from Compston and Coles, 2008.[19]

4. Clinical Methods of Quantifying Disability

In this project we use gait speed as a measure of severity of MS, based on mobility disability. In fact, clinicians specializing in MS often use the 25 foot walk time as a key measure of progression of the disease. Furthermore, the most common method of quantifying disability in MS is the EDSS, which relies heavily on gait speed.

A. Timed 25-Foot Walk (T25-FW)

The **Timed 25-Foot Walk** (T25-FW) is a quantitative test commonly used by clinicians to measure mobility and leg function performance and is a component of the Multiple Sclerosis Function Composite. It is considered the most well-characterized objective, specific assessment of walking disability, most suitable for in the clinical setting.[25] The patient is instructed to walk 25 feet as quickly as possible, but safely from a starting line to a marked finish line. The time is calculated using a stop watch from the initiation of first step until the subject crosses the finish. The subject is then asked to return to the start in the same manner and the average of the two completed trials is taken.

B. Expanded Disability Status Scale (EDSS)

The Kurtzke **Expanded Disability Status Scale** (EDSS) is the most common method of quantifying disability in Multiple Sclerosis and the most commonly used outcome measure in MS clinical trials. Neurologists assign a patient a Function System Score (FSS) for each of eight Functional Systems which are represented in the EDSS. These Functional Systems were defined by Kurtzke[26] as follows: pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral and other. Each FSS is an ordinal clinical rating scale ranging from 0 to 5 or 6 and the EDSS is an ordinal clinical rating scale ranging from 0, a normal neurological exam, to 10, death due to MS, in half-point increments. Both of these rating scales are subjectively based on the judgment of the examiner, leading to discrepancies in both test-retest reliability as well as inter-rater

agreement.[27] Figure 4 summarizes a depiction of mobility disabilities that relate to EDSS scores to help conceive the values of the EDSS scale.

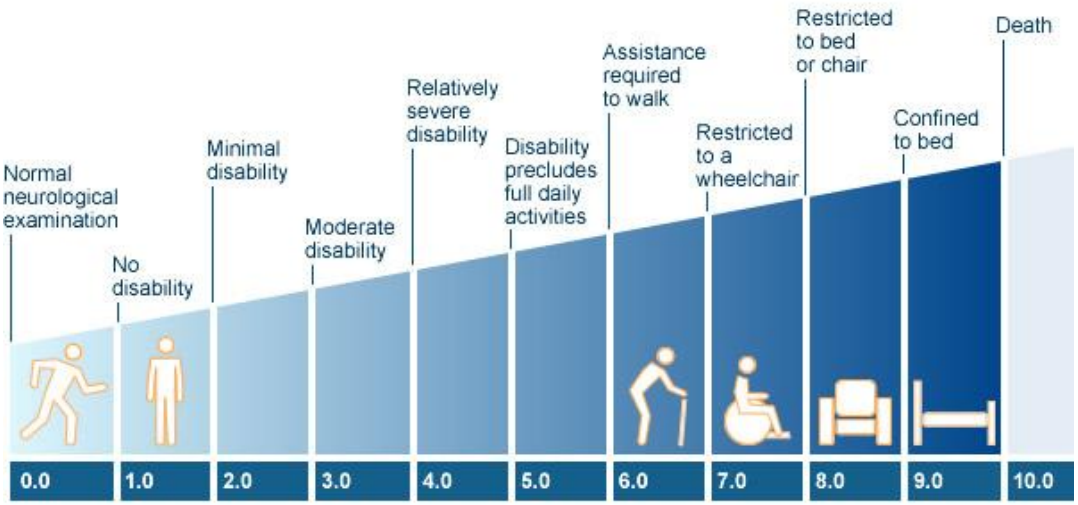

Figure 4. A representation of mobility disabilities across the EDSS scale. Along the bottom are the point values of the EDSS rating accompanied by depictions and descriptions of the disability at that stage. Adapted from Kurtzke, 1983.[26]

Due to the ordinal rating scale of the EDSS, a 1-point difference in one part of the scale does not represent the same interval as a 1-point difference in another part of the scale. Twork S. et al. found that differences between EDSS 4.5-6.5 and EDSS > or = 7 were clearly smaller than the clinical differences between EDSS < or = 4 and EDSS 4.5-6.5.[28] This difference in scales makes interpretation of change or group differences difficult. Furthermore, the EDSS has been criticized by some for an over-reliance on walking distance[29] and limited responsiveness.[30]

Self-reported EDSS questionnaires are becoming more prevalent due to their ease of administration. Several studies have validated self-reported disability scores: Ingram et al. demonstrated an intraclass correlation coefficient of 0.79 between questionnaires

and clinician-derived data in 79 patients, with complete agreement in 75.9%.[31] A French study by Verdier-Taillefer et al. were able to use a linear regression model to predict EDSS scores given by neurologists (+/- 1 point) from patients' answers in 73% of the cases.[32]

See appendix A for clinical meanings of each scale value and for an example of clinical and self-performed EDSS forms.

5. Balance in Multiple Sclerosis

Studies have demonstrated that balance abnormalities are common in patients with MS, whether or not the impairments are clinically apparent. Patients with significant impairments were found to have balance problems, [33] as well as those with minimal impairments, [34][35] and even in the absence of clinical disability.[36] Patients with MS have been shown to have poorer postural control, indicated by greater amounts of postural sway compared with healthy control subjects.[34][35][37][38]. Postural sway has been shown to be related to the patient's relative impairment, as measured by EDSS score. [39] Furthermore, people with MS have been shown to be less able to maintain standing with a reduced base of support [39] and have a reduced ability to move towards their limits of stability and do so less quickly. [33][36][37] One study reported that the majority of the tested patients with MS had delayed postural responses to toe-up postural perturbations and that these delays correlated with prolonged

somatosensory evoked potentials and another study reported slowed automatic postural responses to forwards and backwards displacements in standing mild MS patients. [40][41]

Our laboratory recently published a study demonstrating that subjects with MS who could walk independently without assistive devices had delayed postural responses to backward translations, that these delays correlated with prolongation of spinal SSEP latency, and that these subjects had unimpaired predictive scaling of their postural responses. [11] These findings indicate that imbalance due to MS is caused by extremely delayed postural responses. Furthermore, because of the slowed spinal conduction, somatosensory information about postural displacement is received much later and forces patients to compensate by increasing the use of prediction to scale their responses to the amplitude of an upcoming external perturbation.

Improving balance in patients with MS is crucial for the improvement of quality of life. By understanding the cause of imbalance due to MS, more effective forms of rehabilitation and fall prevention can be developed to improve functional activities and increase well-being. Furthermore, a better understanding of neural control impairments in patients with MS may help explain other symptoms commonly exhibited and better characterize this disease and its progression. The value of early detection of impairments in MS patients, prior to the onset of clinical disability, could allow for the development of earlier therapeutic interventions, and lead to the prescription of drugs that significantly delay the progression of the disease.

Section II – *Balance Control*

1. Background

Maintaining one's balance plays a crucial role in the successful execution of daily tasks and activities.[42] However, balance control is often overlooked because it is mainly conducted on a non-cognitive level and automatically integrated into our voluntary movements and actions. Even though balance is controlled subconsciously, it involves a complex interaction between the musculoskeletal system and sensory systems of the body, including somatosensory, vestibular, and visual systems.

Two forms of postural equilibrium, more commonly referred to as balance, exist: static and dynamic. Static equilibrium pertains to a steady-state balance in which the sum of external forces is completely counteracted by internally generated forces, mostly generated by muscles, resulting in no change, disturbance, or movement of the body. Dynamic equilibrium is associated with walking and other movements which are performed in a controlled manner, ensuring that the center of mass remains within the base of support, averting a fall.[43]

The body is comprised of many linked segments such as arms, legs, and vertebrae that move relative to each other, creating a complex task of constantly remaining balanced. In order to remain upright, the nervous system controls the position and motion of the body's center of mass. The center of mass (CoM) of the body is a hypothetical point that

represents the average position of the body's total mass and is used to help simplify the analysis of external forces acting on the body. In order to remain in a state of balance, the net force on the CoM must equal zero.[44] For example, when someone is in quiet stance (QS), defined as an upright standing position in which the subject is as still as possible, while looking straight ahead, gravity is acting on the center of mass in a downward direction while as the normal force from the ground is pushing upwards with the same amount of force, counteracting gravity and leaving the body in a balanced state. While maintaining a QS, the CoM of a person is located 20mm anterior to the second lumbar vertebra. However, the CoM can also be located outside the body, such as during dynamic tasks of leaning over to pick an object off the ground or while walking.[45]

2. Postural Sway

In this project, we use postural sway area in the forward-backward direction as a measure of severity of impairment of postural control. Previous research has shown that people with MS have increased postural activity during quiet standing as quantified by increased CoP sway.[46][47]

During standing, balance is achieved when the center of mass remains within the base of support. The base of support (BoS) is defined by the parts of the body that are in contact with the environment.[48] In QS, the BoS is delimited by the area beneath and between the two feet, creating a relatively rectangular shape. If a person were to use a

cane to walk, the base of support would be represented geometrically by a triangle, defined by the three points of contact with the ground: each of the two feet and the cane.

Even in QS, the body is in constant motion. In fact, very small postural shifts from front to back and side to side, commonly referred to as postural sway, constantly take place. Postural sway is primarily caused by the inability of the neuro-muscular system to maintain a constant tension [49] as well as partially by respiratory and cardiac muscle contractions.[50][51] For this reason, QS is said to be quasi-static and requires constant muscle corrections to stay upright. In order to reduce the amount of sway that takes place, muscles are often found in a low tonic state, creating a somewhat stiff system less prone to movements. The soleus and ilipsoas (deep flexor muscles) are most commonly used in QS for small corrections, with intermittent activation of the tibialis and large hip and thigh muscles.[52]

3. Postural Responses

In this project, we use postural response latencies as a measure of severity of slowed somatosensory conduction for postural control due to MS. Prior studies in Dr. Horak's laboratory have shown that patients with MS show significantly delayed postural responses to surface translations and these delays are strongly related to their delayed somatosensory evoked potentials from the foot to the top of the spinal cord.[11] We will use the relative delays in postural response latencies to categorize MS subjects into

mild (normal latencies) versus moderate/severe (significantly longer than normal latencies).

It is often thought that responses to sudden disturbances are simply part of a reflex pathway because they subjectively feel automatic and extremely fast. In fact, automatic postural responses involve a complex activation of specific groups of muscles, in a particular time sequence, in order to maintain balance. Humans have response latencies of approximately 70-100ms as measured by electromyography (EMG) from the lower limbs, during a sudden support surface movement, disrupting equilibrium. These latencies are much longer than would be expected of a reflex response and are indicative of a much larger circuit which includes the CNS and the brain.[43][45]

We hypothesize that patients with MS are more likely to adopt a hip strategy over a larger range of postural sway frequencies than controls during quiet standing. This is due to slowed somatosensory conduction from the feet and ankles, which leads to the use of delayed information for balance correction, as well as delayed postural motor actions. Hip strategy muscle somatosensory input may have a much shorter neural distance to travel and results in faster movements of the body's center of mass making it a more timely and dependable mechanism for balance control when somatosensory inputs are delayed.

4. Sensory Integration

This project examined quiet stance, which requires complex integration of somatosensory, vision, and vestibular information for postural control. Control subjects depend primarily upon somatosensory information to control postural sway although they can increase dependence upon vision and vestibular information when somatosensory is unavailable on an unstable surface. However, in people with MS, somato-sensation, especially in the feet, is impaired due to demyelination of spinal and supraspinal axons in sensory pathways. MS patients with delayed and distorted somatosensory inputs would be expected to give more weight to visual and vestibular information for postural control, even though the visual and vestibular inputs can also be partially impaired in some patients. When MS subjects close their eyes, they lose another important source of sensory control of postural, resulting in much larger than normal postural sway because vestibular sensory information is noisy.

Each of these three sensory modalities contributes to determine the body's orientation, to evaluate the effects of external forces, and to predict and avoid potential disruptions of balance. Although each sensory system provides different information, there is enough redundancy among the three senses that loss of one input does not prevent the ability to accomplish postural tasks.[43] This is perhaps most apparent when one tries to walk in the dark. Although the visual system in the dark provides minimal information to the brain, the vestibular and somatosensory modalities (such as touching the walls for further input) are able to provide enough information to navigate to the desired

destination. The importance of having multiple channels of input is to resolve ambiguities in sensory information.[53] For example, the visual system determines movement based on images slipping across the retina. However, this is only able to distinguish relative, but not absolute, movement. This has most likely occurred to everyone at least once; while sitting on a bus or in a car, you are looking out the window and at some point you feel like you have started moving. Yet when you turn your head and look forward, you notice that you are still stationary. As you look back out the window, you realize that in fact, it was the car outside that had started moving. This is an example of sensory information that is ambiguous and interpreted incorrectly due to lack of other sensory input but is quickly rectified by new visual input, or the realization of the lack of vestibular information conveying body acceleration.

These two examples also demonstrate the way in which the brain weighs sensory input. In the dark, your visual system is providing very little information; therefore, the brain prioritizes information from the vestibular and somatosensory systems to help maintain balance. Similarly, while stationary in a car, the somatosensory and vestibular information is remaining constant, which causes a strong weighing of the visual modality. Various weighing of sensory information is commonly seen in patients who have deficits caused by some injury or disease to one of their inputs, allowing them to cope and carry out daily tasks. The amount any particular MS patient depends on each sensory modality will depend on which sensory systems are providing accurate, timely information. Since most MS patients have long track damage in spinal cord, we suppose

they would usually down-weight their abnormal somatosensory inputs and increase dependence on their vestibular and visual systems.

A. Vestibular Information

The vestibular system consists of the semicircular canals and the otoliths, which are found approximately at ear level within the skull. The semicircular canals are sensitive to angular accelerations of the head, such as turning or tilting. These play an important role in detecting high frequency postural sway but are less sensitive to low frequency sway found in quiet stance.[43] The otolith organ detects linear accelerations and provides information about gravity and body tilt during quiet stance. The vestibular system appears to be crucial in stabilizing the head in space and coordinating head movements with other body movements in order to remain balanced.[54] Furthermore, vestibular information plays a pivotal role for balance when both visual and somatosensory information is reduced such as with eyes closed on an unstable support surface.[43] Although MS can sometimes affect central vestibular pathways, our study excluded subjects with known vestibular deficits or dizziness.

B. Somatosensory Information

Somatosensory afferents are vital to balance because they provide information about postural orientation. These afferents include cutaneous mechano-receptors and proprioceptive receptors in muscle fibers, tendon organs and joints. Cutaneous receptors are found everywhere on the body, but those under the soles of the feet contribute most to balance as they sense pressure changes associated with body sway.

Proprioceptive receptors provide information about positioning of various body parts, compressive forces on joints, and the stretch of muscles. All this information is consolidated and helps create and update the internal representation of the body. Moreover, Horak and colleagues concluded that somatosensory information from the feet helps determine feasible postural strategies for a particular condition, and that without this information, ankle strategy could not be used so subjects compensate with the hip strategy.[55] MS patients have delayed conduction of somatosensory pathways up the spinal cord to the cerebellum and cortex and their postural responses are delayed in proportion to the slowing of somatosensory conduction, so we hypothesize that MS will be associated with increased use of hip strategy for control of postural sway.

C. Visual Information

The visual system provides information to the brain about orientation and motion. This is exemplified by the fact that body sway during quiet stance maybe increased when eyes are closed. Body sway greatly increases with eyes closed in patients who have impaired somatosensory or visual inputs, such as occurs with MS.[47][48][57] However, MS can also affect visual pathways, although this is less common and subjects with known visual deficits were not included in our study.

5. Balance Response Strategies

Humans use three movement strategies to keep their balance during daily activities. Each of these three strategies is utilized to produce the forces necessary to maintain control of the body's CoM over its base of support. The use of individual strategies, or combinations thereof, is determined by many different factors including, but not limited to velocity, size, and direction of the disturbance; initial position and orientation of body segments; prior experience; environmental factors; and the availability of sensory information.[58] Furthermore, each strategy has biomechanical limitations and effectiveness in particular situations, which also help dictate its use. For example, the ankle strategy requires more ankle torque than the hip strategy so ankle weakness in patients with MS would result in more use of a hip, than ankle, strategy.

The most commonly used strategy during quiet standing is the ankle strategy. As the name suggests, this strategy creates torque primarily around the ankle joint, with little hip or knee motion. This strategy is most often seen during quiet stance, in the presence of small and slow perturbations, especially when on a firm, even surface. Since the torque applied is relatively far from the CoM, the ankle strategy is limited to lower frequency adjustments below 1 Hz.

The hip strategy is slightly more complex than the ankle strategy. Not only does the body rotate at the hips to move the CoM, but this strategy is accompanied by counter-rotation of the neck and ankles in order to keep the head in facing forward and the CoM over the feet. The hip strategy is most commonly seen in response to large or rapid

perturbations or when the surface does not allow adequate torques to be exerted for the ankle strategy. Loss of somatosensory information from the feet in subjects with MS may be interpreted by the nervous system as an unstable surface, resulting in increased use of the hip strategy.

The third type of postural movement strategies the stepping strategy. In a normal subject the stepping response is seen with very large disturbances, considered too large to be effectively compensated by either of the other strategies. The purpose of taking a step is to widen and move the base of support under the falling body CoM.

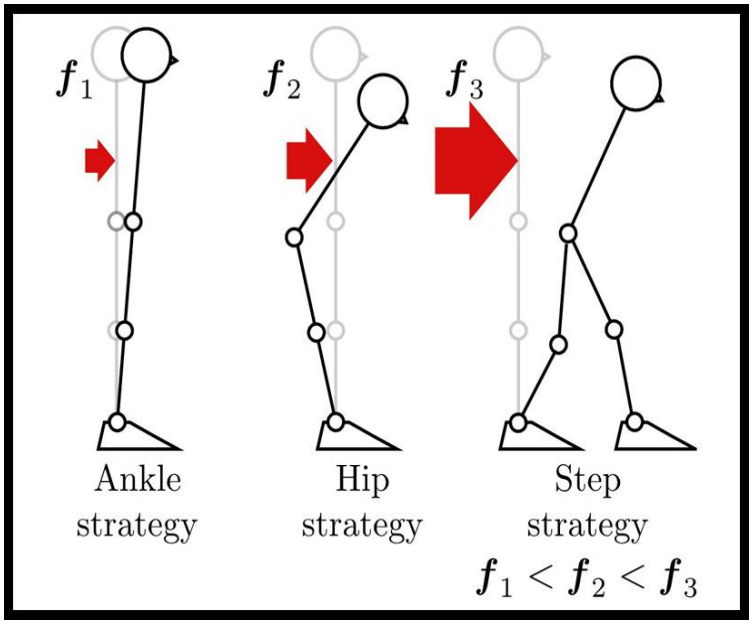

Figure 5. The three strategies used to maintain balance during quiet standing. (A) The use of ankle strategy involves only the movement at the ankles as the rest of the body remains rigid, like an inverted pendulum. (B) The hip strategy is comprised of a bending at the hip accompanied by counter-rotation at the ankles. (C) The stepping strategy is used in response to large perturbations.

These three strategies are used both in quiet stance as well as disturbed stance. Previous studies found no increase in sway area during quiet stance following loss of somatosensory information from the feet and ankles alone by ischemia below the knees, but a significant increase of sway was found when proprioceptive inputs from leg muscles was impaired by ischemia above the knees.[59] Subjects with somatosensory loss due to peripheral neuropathy also used increased hip strategy when displaced.[60][59] Somato-sensation and vision have been shown to play distinct roles in stabilizing body segments during quiet standing. Disturbance in somatosensory input using a moveable platform caused a highly significant increase in hip strategy.[61] These results suggested that the ankle, but not the hip strategy, requires somatosensory information from the feet.[62] Elderly patients were also found to have increased use of hip strategy during platform sway-referenced conditions, hypothesized to be due to sensory noise or decreased ability to detect small motions of the platform due to poor proprioception.[63]

6. Ankle versus Hip Strategy

Human upright stance during quiet standing has typically been modeled as a single segment inverted pendulum.[64] This model was established based on a large body of research suggesting that balance in quiet standing is maintained by means of the ankle strategy. Therefore, the pivot of the body is taken to be the ankles, and the rest of the body is modeled as an unbending segment.

However, investigations involving applications of external force or altered visual stimuli have shown that the body behaves like a double-inverted pendulum, with fulcrums at the ankles and hips. Furthermore, the upper and lower body display both in-phase and out-of-phase oscillations during quiet stance, exhibiting features of both single- and double-pendulum features, respectively. Creath et al., in our laboratory demonstrated that during quiet stance, ankle and hip strategies were not extremes in maintaining balance but rather were co-existing, creating a continuum of mixed strategies.[65]

Creath and colleagues identified balance strategies in the frequency domain using the coordinative relationship between trunk and leg segments by analyzing the cophase between ankle and hip angles. The in-phase and anti-phase relationships are indicative of the ankle and hip patterns respectively. This shift from in-phase to anti-phase was also noticed when considering coherence, but to a lesser degree.[65] Their study found simultaneous existence of in-phase (generally for frequencies below 1Hz) and anti-phase (typically frequencies above 1Hz) relationships between leg and trunk angles, which allowed investigators to determine the relative use of the ankle and hip strategies among individual subjects. The trend to use more hip and less ankle strategy when standing on foam and sway-referenced surfaces than on a firm surface are depicted below in figure 6A and B from Creath et al.

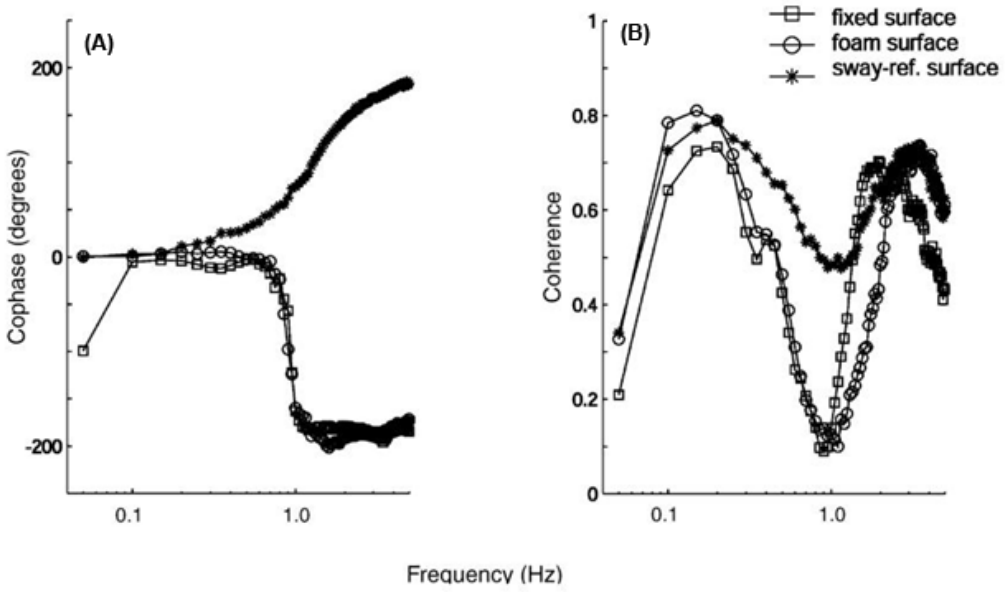

Figure 6. Cophase and Coherence plots between the ankle and the hip, in the frequency domain. (A) Cophase shows a rapid change from in-phase to anti-phase motion, signifying a change from ankle to hip strategy around 1Hz. (B) Coherence demonstrates a high coherence at the lower frequencies followed by a drop to nearly zero at 1Hz, indicative of a strategy change (from Creath et al, 2005).

This was a very important discovery because it unified the relationship between quiet and perturbed stance. As a result, this implies that multilink inverted pendulums is a more accurate model for quiet stance and that balance is a continuous combination of both hip and ankle strategies.[65]

Several methods have been used in the literature in order to determine active balance strategies. Force-plate based computations predicting CoM along with generic anthropometric data is a validated a method of estimating ankle and hip strategies for a double-inverted pendulum model.[66] However, covariance measures of ankle and hip angles based on kinematic recordings of displacement are most often used to determine balance strategies.

7. Methods of Investigation of Balance Strategy

Most investigators use rapid and brief perturbations in order to study immediate postural reactions associated with balance control. An alternative testing method involves application of force to the upper body segments, such as pushing or pulling the trunk or pelvis.[67][68]

This section consists of a brief overview of several popular techniques for measuring balance. By no means is this list comprehensive, but they represent the main categories which are utilized in the examination and study of posture and balance.

A. Force Platforms

Force platforms are a commonly used instrument for the analysis of posture via kinetics. These platforms record the body's ground reaction force which acts on the foot while standing, and are required in order to maintain upright posture, counteract gravity, and compensate for external forces. This force vector consists of three components, one in each orthogonal dimension and is strongly correlated to the displacement of CoM through the center of pressure (CoP) measure. Kinematic information includes the recording of CoP, reactive torques, and shear forces applied to the surface, as a function of time, to maintain balance.

B. Motion Analysis

Kinematics refers to the description of human movement and is not concerned with forces, either internal or external, that cause the movement, but rather the particular

movements themselves. Specialized optical motion analysis systems are able to measure the body's movement. For example, the system used in Fay Horak's Balance Lab at OHSU consists of eight infrared cameras mounted to the ceiling and dispersed equally around the room. Small reflective markers, which are tracked by the motion analysis cameras, are then placed on the patient in anatomically significant positions, allowing for the creation of a three dimensional spatial body representation in time as well as measurements and calculations of CoM and segmental motion.[69] Software using triangulation allows for extremely accurate measurements of position of each individual marker in space. With the help of reference points, a three dimensional representation can be created by the computer as shown in Figure 7, on the following page.

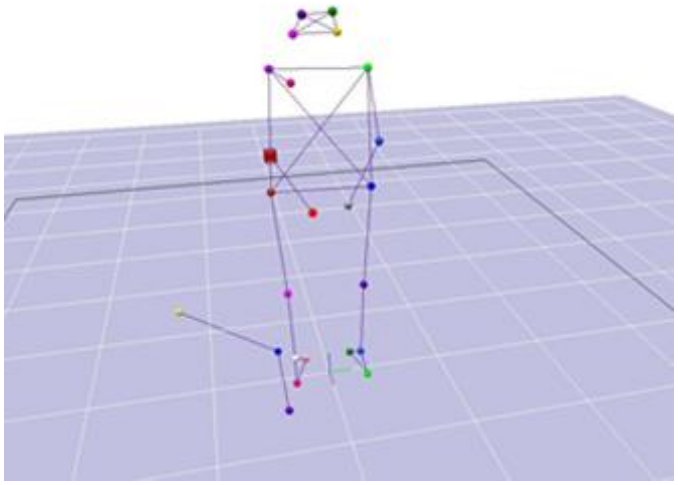

Figure 7. An example of a 3D representation of kinematic data collected.

These systems capture information at relatively high frequencies, ranging from 50Hz to 120Hz or more. In essence the motion analysis gives 3D coordinates of each individual

marker in a given space, over time. This allows for the determination of displacement, which is merely the shortest distance from the initial to the final position of a point. One can calculate a marker's velocity by taking the first derivative of displacement, acceleration with the second derivative, and jerk with the third derivative. Angles, angular velocities, and angular accelerations can also be calculated between markers. The angle can either be determined relative to plane, such as the horizontal or vertical (gravity), requiring two points, or the calculation of a joint angle for example, requiring three points.

This recording technique is considered the gold standard when it comes to posturography experiments.

C. Accelerometers

Accelerometers, as the name suggests, are devices used to measure accelerations. Many of these devices are simply force transducers designed to measure reaction forces attributed to a particular acceleration. Hence, a small mass within the accelerometer creates a recorded force when movement occurs. Using Newton's Second law, F=ma, one is able to calculate the acceleration since the force is measured and the internal mass is known. Many accelerometers are three-dimensional, recording accelerations in each of the three orthogonal dimensions, and are simply composed of three individual transducers. Accelerometers have become much more prevalent in recent years due to their light weight form factor, relatively inexpensive purchasing costs, measurement accuracy, and abundance of extracted information. The addition of temperature sensors

and magnetometers allows for more accurate measurements and can help correct for drift experience during long experiments without recalibration.

Section III – *Effects of Multiple Sclerosis on Balance*

The study of balance and gait in Multiple Sclerosis has been mostly neglected, with only a relatively small number of studies conducted. The science of balance and gait is mature and current computer posturography and motion analysis has been around since the 70s. A large portion of this research has been conducted to understand what is considered normal balance and gait in young, healthy adults. Similarly, older healthy adults have been studied in an effort to document the effects of aging on balance and gait. A subset of research has also emerged which focuses specifically on subjects with abnormalities, often due to disease, such as vestibular loss or Parkinson's disease.

Balance and gait studies in MS have largely focused on improvements on a patient's physical performance when taking a particular drug or conducting exercise regiments[70] as well as predicting future falls as a means of early prevention.[71][72][71][66][67] In the past decade, researchers have begun to investigate the specific deficits in balance characteristics, such as sway area, as well as the underlying causes of these problems. For example Sosnoff et al. found that patients with MS who had high spasticity were also found to have greater CoP area, velocity, and mediolateral sway compared with the low spasticity and control group which suggests

that spasticity contributes to postural deficits observed in MS.[75] Spain et al. also looked at balance in people with MS who have normal walking speed and were able to detect balance deficits using body-worn motion sensors.[76] However, neither of these studies, nor any other study, has investigated the balance strategies used to control upper and lower body movements that underlie the larger sway area found in subjects with MS.

Only a handful of quiet standing studies have been conducted in patients with MS and only one paper to date has addressed change in balance strategies in patients with MS. [77]

The primary aim of this research is to determine whether subjects with MS use different balance strategies compared to normal controls during quiet standing. Traditionally, quiet stance is modeled as a single inverted pendulum, called an 'ankle strategy' while as perturbed upright stance shows characteristics of both single and double inverted pendulums as a result of the introduction of 'hip strategy'.[78] However, Creath et al. recently it has been shown that healthy subjects use passive stiffness and tonic ankle activity [79][80] and a double inverted pendulum strategy simultaneously while standing.[64][65]

It is possible that patients with MS have abnormal kinematic strategies during quiet stance because of their poor conduction of proprioceptive inputs up the spinal cord. Cameron et al. recently examined the latency and scaling of automatic postural responses and their relationship to somatosensory evoked potentials and suggested

that imbalance in MS could be a result of slowed spinal somatosensory conduction.[11] In addition, previous studies have shown that patients with somatosensory loss due to peripheral neuropathy use more hip strategy to recover from postural perturbations than healthy subjects. Efforts in determining whether loss of proprioceptive inputs from MS would also results in increased dependence on the hip strategy or postural control during stance have yet to be conducted. *We hypothesize that subjects with MS who have proprioceptive loss would show more hip strategy in coherence and cophase when compared to control subjects.*

Chapter 2 Material and Methods

1. Participants

Thirty-seven subjects with Multiple Sclerosis (mean age 46±12) with ranging degrees of severity (self-reported EDSS 19±7.5) and 21 healthy controls of similar age participated in this study. All participants were recruited through the Multiple Sclerosis clinic at OHSU. Subjects were selected such that they would be able to complete the study and did not have any other condition that could affect their balance or gait. No restrictions on the type of MS were implemented in this study. All participants provided informed consent according to the Oregon Health & Science University, Institutional Review Board.

2. Experimental Protocol

The participants were asked to come in to the lab early in the morning and to bring comfortable clothing as well as shorts, which they wore for the duration of the experiment. Subjects were equipped with 24 motion analysis markers and 6 inertial sensors, and they stood on a movable force platform for the following motor tasks:

1) Quiet Stance

Subjects were asked to stand quietly with arms folded across their chests in a comfortable position and with their feet 10cm apart. Twelve 30 second trials of quiet

standing were performed, consisting of four different conditions: (i) eyes open (EO), (ii) eyes closed (EC), (iii) eyes open counting (EOC), (iv) eyes closed counting (ECC). In the eyes open condition, patients were asked to focus on a poster in front of them, 5 meters away, directly in front of them for the duration of the trial. The two counting conditions involved patients standing quietly while counting backwards by threes from an arbitrarily selected number. The order in which each condition was performed was randomized between patients and comprised of three total repeated trials for each condition. For example, a patient might first be asked to perform three EO trials, followed by three ECC, then three EC, and finally three EOC. Initial stance condition was consistent from trial-to-trial by tracing foot outlines with tape on the force platform.

2) Forward Platform Translation

Subjects stood on a force platform, movable in forward and backward directions under the control of a hydraulic servomotor, with heels 10cm apart, and were told to try to maintain their balance as best they could. These perturbations displaced the center of body mass in the opposite direction of the feet, such that a forward platform movement resulted in a backward body sway. The first three trials consisted of slight, abrupt forward translations of the platform. The distance and acceleration of the platform were big enough to require reactionary responses but small enough as to not elicit a step. Similarly, the following three trials were performed with a backwards translation of the

platform. Bilateral EMG recordings of the tibialis anterior and gastrocnemius were collected only during these trials in order to determine response latencies which were later used to subdivide patients for analysis.

At the end of the data collection, MS patients were then asked to fill out a self-reported Expanded Disability Status Scale (EDSS), an Activities-specific Balance Confidence Scale (ABC), and a Multiple Sclerosis Walking Scale-12 (MSWS-12).

3. Equipment

Twenty-four reflective markers were attached to the skin or tight fit clothing, using transparent, perforated plastic tape demarking symmetrically the: (i) superior zygomatic arch, (ii) lateral mandibular joint, (iii) acromion process, (iv) olecranon, (v) styloid process, (vi) anterior superior iliac spine, () iliac crest, (vii) lateral femoral condyle, (viii) lateral malleolus, (ix) fifth metatarsophalangeal, (x) calcaneus, and (xi) the right scapula. Figure 8A is a representation of marker positions to help visualize where markers were placed on subjects. Three additional markers were placed in specific positions on the floor as a frame of reference. Motion Analysis system used 8 Falcon Cameras evenly distributed around the lab, capturing at 60Hz.

Six MTX Xsens inertial sensors (49A33G15, Xsens, Enschede, NL), containing 3D accelerometers (± 1.7 g for lumbar and 5g otherwise), 3D gyroscopes (± 300º/s range), and 3D magnetometers mounted on: (i) sternum, 2cm below the sternal notch, (ii)

sacrum (L5 level, approximately at the body's center of mass), (iii) on the dorsum of the right and left wrist, (iv) right and left lower leg, 4cm above the malleolus. Figure 8B illustrates the relative positioning of the sensors on the body. The sensing axes were oriented along the anatomical antero-posterior (AP), medio-lateral (ML) and vertical (V) directions.

Motion analysis, force platform, and inertial sensors data were simultaneously collected with a custom synchronization.

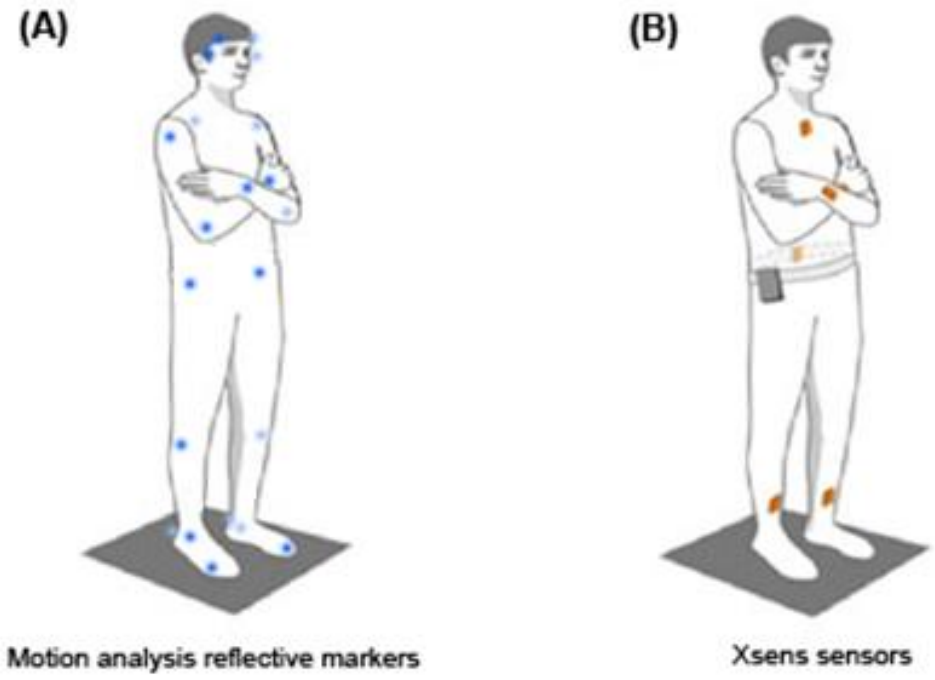

Figure 8. Representation of marker and sensor positions for data collection. (A) Placement of the 21 body worn reflective markers used for kinematic recordings using motion analysis. Dark orange markers are markers in the foreground light orange are covered by the body. (B) Placement of the 6 Xsens sensors around the body providing acceleration data.

Only accelerometry data from the sternum, sacrum, and lower leg, collected at 50Hz, were used for analysis. Similarly, only positional information from the shoulder, hip, and ankle markers, gathered by the infrared motion analysis system were used.

4. Data analysis

A. Pre-Processing

Kinematic data collected by the motion analysis system underwent pre-processing using Cortex version 1.1.4 software by Motion Analysis. This program allows for the visualization of the data collected in various ways including a 3-dimensional representation and xyz coordinates of each marker over time (frames). Figure 9 is a screenshot of the Cortex interface used for pre-processing.

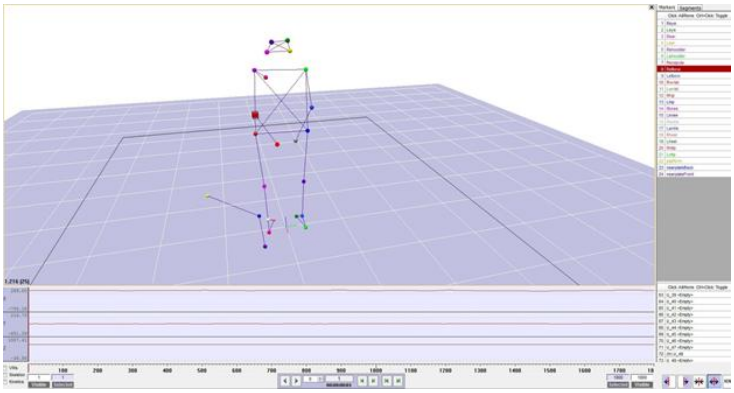

Figure 9. Screenshot of the Cortex interface containing a 3 dimensional representation of the subject with x, y, z displacement data of each marker over the entirety of the trial.

Each trial, for every patient, initially is a collection of black dots in space, recognized by the cameras. Experimenters, after data collection is complete, individually assign each marker a label (for example, Right Scapula or Left Shoulder). Once each marker has been assigned, Cortex extrapolates the labeling of the reference frame across the entire trial, which in this case is 1800

frames for a 30 second trial at a capture rate of 60Hz (60 frames a second). Once all markers are labeled appropriately, Cortex is able to use a defined template to connect appropriate body markers, creating a skeletal representation of the subject during the trial as seen in figure 10B.

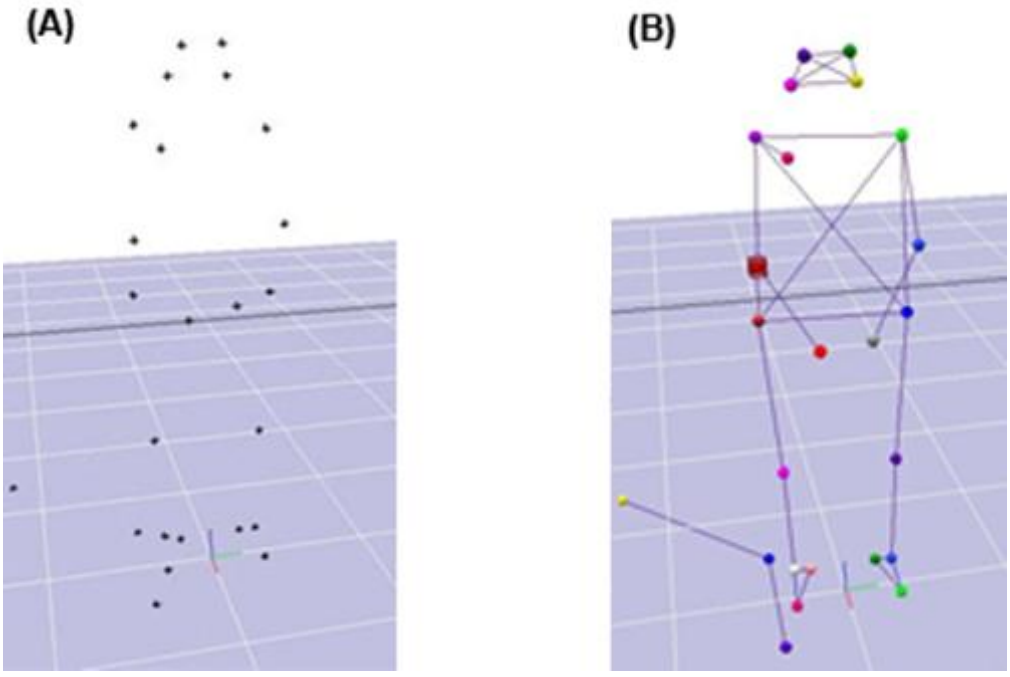

Figure 10. Example of the computer representation of collected kinematic data using motion analysis reflective markers. (A) Raw marker data prior to the introduction of marker labels and the human model template. (B) Post marker labeling and establishing a template allowing for the correct connection of markers.

The experimenter then methodically reviews each trial. Particular labels will often be found on incorrect markers and must manually be corrected in each incorrect frame. Alternatively, a marker might disappear for a few frames caused by being covered up by clothing or temporarily not in the line of sight of at least three cameras. In these cases the experimenter uses a function called join cubic which predicts a marker's location based on a cubic function of the surrounding frames. If a marker is not detected for more than eight frames, a function named join virtual was used which utilizes other defined markers; one as the origin, one as a long axis and another as a plane marker.

The three reference markers were selected based on provided laboratory guidelines. For markers which were unavailable for extended periods or non-existent in a given trial were noted and said trial was potentially excluded from further analysis. Once a trial was satisfactorily devoid of problems, a smoothing function was use which acted as an initial low-pass filter for any non-physiological noise. Figure 11 illustrates two common required pre-processing corrections, namely mislabeled markers and a missing marker.

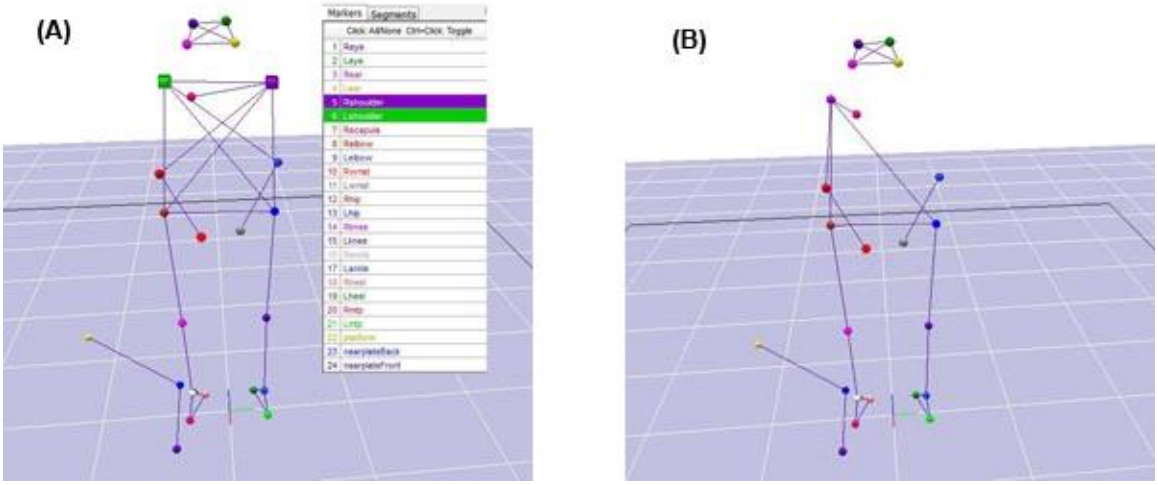

Figure 11. Two examples of commonly encountered problems during pre-processing. (A) A case in which the right and left shoulder have been mislabeled as the other. This causes the model to be inaccurate, with marker connections crossing the body, such as the shoulder marker on the right side connected to the hip and elbow markers on the left side. (B) A sample situation in which the left shoulder marker is absent leading to an incomplete subject model.

Displacement data gathered by the motion analysis system, after initial pre-processing using Cortex, were then imported into Matlab. Due to the higher sampling frequency of the motion analysis, matlab's resampling function which applies an anti-aliasing (low-pass) FIR filter using a Kaiser window.

Accelerometry data collected by the Xsens sensors in the three coordinate axes were imported into Matlab. A trigonometric correction was used in order to adjust the acceleration data to a horizontal-vertical coordinate system, as described by Moe-Nilssen et al.[81] The algorithm designed by Moe-Nilssen and colleagues is based on the assumption that the best estimate of the mean acceleration over a period of time, during undisturbed, quiet standing, will be zero along any axis. Any measured mean acceleration deviating from zero is assumed to be cause by the effects of gravity due to the constant tilt of the measurement axis. If the tilt angle is denoted by α, with the upwards direction designated as positive, the gravity factor will be equal to g sin α, where g = 1 in units of gravity. Therefore, if measu $_A$ is calculated in units of gravity, the tilt angle can be found as well as the true acceleration along that axis.

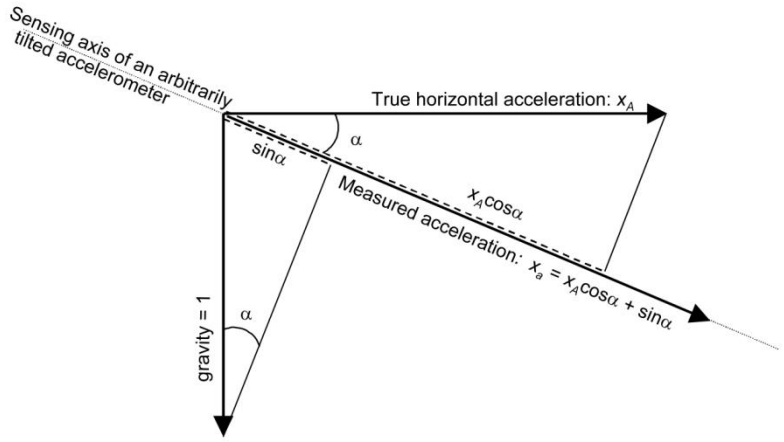

Figure 12. Illustration of the concepts used by Moe-Nilssen to correct for tilted accelerometer placement on subjects. Shows the relationship between the measured acceleration (x_a), along an arbitrary axis (tilt angle α) and the true horizontal acceleration (x_A). The measured acceleration is equal to the vector sum of its vertical gravitational component and its horizontal component. Adapted from Moe-Nilssen & Helbostad, 2002. [81]

After correcting for the tilt, accelerometry data for each axis were filtered with a 3Hz cut-off, zero phase, low-pass Butterworth filter.

Both the kinematic and accelerometry data were then visually inspected to ensure correct recordings and outliers were removed before calculating power spectrum. For this purpose, unfiltered hip and ankle angles were plotted against time when looking at kinematic data as well as accelerometers data from ankle and lumbar sensors. These figures allowed for a quick visualization of signals which were physiologically unlikely or impossible (for example sometimes we found a sudden change at the beginning of a trial, probably due to inadvertent movements of the participant). Some files were corrected, while others had problems relating to equipment or patient cooperation (such as moving before the end of 30 seconds), which were then discarded from both kinematic and accelerometry analysis. Criteria for exclusion included trials with incomplete data collection, missing portions of data, extremely noisy recordings post filtering, and physiologically impossible actions or findings. If a trial fell within any of these categories, it was removed from both the kinematics and accelerometry analyses. Forty-three trials in total were discarded and omitted from calculations, for various reasons.

B. Features extraction

Trunk and leg angles relative to earth vertical were calculated using the measures of AP shoulder and hip displacement for the trunk segment and AP hip and ankle displacement for the leg segment. Trigonometry was used to calculate trunk angle and

leg angle at every time interval. This was achieved by simply taking the arctangent of the difference between the vertical positions (either shoulder-hip for trunk angle or hip-ankle for leg angle). The relationship between angle and body segments is diagrammatically illustrated below in figure 13.

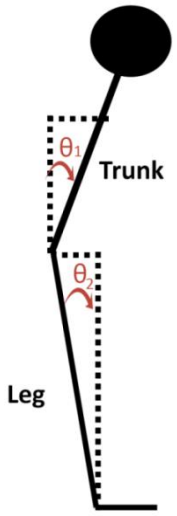

Figure 13. Demonstration of the trigonometric concept used to calculate trunk and leg angles. Θ_1 represents the trunk angle and θ_2 the leg angle, where the Angle θ = ———— .

After both angles were calculated at each time interval, the angles were passed through the same 3Hz cut-off, zero phase, low-pass Butterworth filter as the accelerometry data.

The power spectral and cross-power spectral densities (PSD and CPSD respectively) were independently calculated from the filtered anterior-posterior accelerations and angles using matlab's built in functions. The PSDs and CPSD were calculated with the Welch's averaged method. An Hanning window size of 4 seconds with an overlap of 50% was used for both calculations. Welch's method is a spectral density estimation used for estimating the power of a signal at different frequencies. Having overlapping windows of 50% reduces the variance by about a factor of 2, owing to doubling the number of

segments.[82] Welch's method is often used because it reduces noise in the estimated power spectra in exchange for reducing the frequency resolution. The complex coherence was then calculated using the PSDs and CPSD by the following equation:

$$C_{xy} = \frac{P_{xy}(f)}{\sqrt{P_{xx}(f) \cdot P_{yy}(f)}}$$

Where $P_{xy}(f)$ is the CPSD and $P_{xx}(f)$ and $P_{yy}(f)$ are the PSDs for the signals being compared. For example, when taking the coherence between the angles of the trunk and leg, $P_{xx}(f)$ could represent the PSD of the leg angle, $P_{yy}(f)$ the PSD of the trunk angle, and $P_{xy}(f)$ the CPSD of the trunk and leg. The complex coherence can be thought of as a sort of correlation coefficient in the frequency domain between two signals.
Means of the coherence of each of the three trials for each condition were taken (ex: average of trials 1-3 for EO) and then means of each condition across every patients in a particular group were taken.

As suggested by Dr. Peterka, we looked at the frequency at which the Cophase between the trunk and leg segments crossed 90°. The change in-phase to anti-phase marks a change in strategy at different frequencies. The choice of 90° was a somewhat arbitrary value but was chosen because a peak in cophase is more difficult to define on a per subject basis. 90° crossings were determined for each patient on the mean of three trials of a given condition (ie 90° was found for the mean of three EC trials). Crossings were defined as the frequency which: (1) is immediately preceded by a point below a value of 90, (2) is greater than 90, and (3) is greater than the preceding point. This

ensured that the point found was at an increasing cophase crossing 90°. The value of the corresponding coherence was also recorded. In addition, we also looked at the frequency at which the minimum value of the coherence occurs. This was potentially another marker that could be used for determining at what frequency balance strategy changes. A low coherence between trunk and leg, along with anti-phase motion can be defined as the increased use of hip strategy. The minimum value of coherence was found for each patient based on the mean of three trials of each condition. The frequency of this point was recorded along with the value of the cophase at that frequency.

C. Group Classification

Patients within the MS group were divided by severity into mild and moderate groups. These subdivisions were based on three different criteria: 1) the 25 foot walk (patients who took less than 5 seconds were classified as mild), 2) EMG latencies after a perturbation (those within two standard deviations [22.06ms] from the control mean [107.99ms] were classified as mild), and 3) anterior-posterior sway range (patients within two standard deviations [20.24mm] from control means [26.32mm] were classified as mild). The 25 foot walk was chosen as a way of determining severity because it is the most commonly clinical measure used. When classified by the 25 foot walk, initially 20 subjects were in the mild MS group and 17 in the moderate MS group. Dividing subjects by latency yielded 15 in the mild MS group and 22 in the moderate

group. When segregated by sway range, 23 subjects were placed in the mild MS group and 14 in the moderate MS group.

5. Statistical Analysis

Analysis consisted of means of three adjacent values of either coherence or cophase, with the exception of the first bin for which the first coherence and cophase values were omitted, leading to the mean of only two values. A second method was used in addition on a subset of data sets which involved only the value at particular frequencies instead of taking the means. Sixteen mean frequencies were analyzed): (1) 0.0333-0.0667, (2) 0.1-0.1667, (3) 0.2-0.2667, (4) 0.3-0.3667, (5) 0.4-0.4667, (6) 0.5-0.5667, (7) 0.6-0.667, (8) 0.7-0.7667, (9) 0.8-0.8667, (10) 0.9-0.9667, (11) 1.0-1.0667, (12) 1.1-1.1667, (13) 1.2-1.2667, (14) 1.3-1.3667, (15) 1.4-1.4667, (16) 1.5-1.5667. For simplicity, these frequency intervals will be referred to either by their ordinal interval position, such as frequency 1 refers to 0.0333-0.0667Hz, or by the middle frequency of the interval, such that frequency 0.53 refers to the interval 0.5 to 0.5667.

Comparisons were performed on mild MS versus moderate MS, mild MS versus controls, and moderate MS versus controls, using three separate classification criteria (latency, walking speed and sway range) and in both kinematics and accelerometry. A repeated measures ANOVA was conducted using both 3 group separations (Mild vs Moderate vs Control) and 2 group separations (MS vs Control).

Comparison of eyes open versus eyes closed, within subject groups, of the frequency at which the 90° crossing in cophase occurs, as well as the value of the coherence at that frequency, were carried out using repeated measures ANOVA. This analysis was performed on mild MS, moderate MS, MS (mild and moderate combined), and controls, classified by latency, walking speed, and sway range using only kinematics.

Within-group analyses of frequency were carried out in order to determine at which frequencies coherence was significantly changing. Coherence and cophase were binned at 10 different frequencies for this analysis. As before three values were used for each bin which were found at: (1) 0.2-0.2667, (2) 0.3-0.3667, (3) 0.4-0.4667, (4) 0.5-0.5667, (5) 0.6-0.667, (6) 0.7-0.7667, (7) 0.8-0.8667, (8) 0.9-0.9667, (9) 1.0-1.0667, (10) 1.1-1.1667. Repeated measures ANOVA was conducted along with post-hoc Bonferroni corrected pairwise comparisons of within-group effects. Analyses were performed on mild MS, moderate MS, MS (mild and moderate combined), and controls, classified by latency and walking speed for kinematics and accelerometry.

Chapter 3 Results

1. Patients with moderate MS showed lower coherence at low frequency compared to mild MS and controls

The following figures show the mean (±SEM) coherence and cophase that describe the relationship between trunk and leg segment during QS under eyes open and closed conditions in MS patients and controls. MS patients were divided into 2 groups, mild and moderate according to 3 different criteria: 1) 25ft walk clinical distinction, 2) latency during postural perturbations (2 SD away from control mean value), 3) amount of sway range during QS eyes closed (2 SD away from control mean value).

The most striking results are:

- the difference between control subjects and moderate MS subjects in coherence at low frequency,
- the difference between mild and moderate MS subjects in coherence at low frequency, and
- the relative similarity between mild and control groups in coherence among all the frequencies.

Tables are provided after each graph, containing statistical results.

A. MS grouping according to Sway Range

Accelerometry

QS Eyes Open

Moderate MS subjects showed significantly lower coherence between the trunk and leg accelerations compared to mild and control subjects below 1Hz (F-values ranging from 11.27 to 17.58, and p-values ranging from 0.0394 to 0.0014 Bonferroni corrected) and in cophase above 1Hz (F-values ranging from 11.21 and 12.98, p-values of 0.0406 and 0.0159 respectively, Bonferroni corrected), see Table 2 and Figure 14-A,B.

In contrast, mild MS showed coherence and cophase similar to control subjects.

Moderate MS subjects showed lower coherence with uncorrected statistical significance compared to mild MS and control groups below 1.2Hz (see Figure 14-A); and higher cophase overall (see Figure 14-B).

In general, all three groups had visually similar trends of constant coherence at low frequencies followed by an increase around 0.5Hz and finally a decrease to a trough around 0.8Hz.

QS Eyes Closed

Similarly to eyes open, in the eyes closed condition moderate MS subjects showed significantly lower coherence compared to control subjects below 1Hz (F-values ranging from 11.81 to 17.23, and p-values ranging from 0.0006 to 0.0000 Bonferroni corrected)

but only an uncorrected significance in cophase above 1Hz, see Table 3 and Figure 14-C,D.

Mild MS showed coherence and cophase similar to controls, as well as during eyes open condition.

Moreover, moderate MS subjects showed lower coherence with uncorrected statistical significance compared to mild MS and control groups below 1Hz (see Figure 14-C); and higher cophase above 1Hz (see Figure 14-D).

In general, when visually comparing the eyes open condition to the eyes close condition, the shape of both cophase and coherence are very similar. Features in coherence, namely the separation between moderate and controls at the lowest frequencies and the peaking of the MS groups around 0.73Hz, become more pronounce in the EC condition.

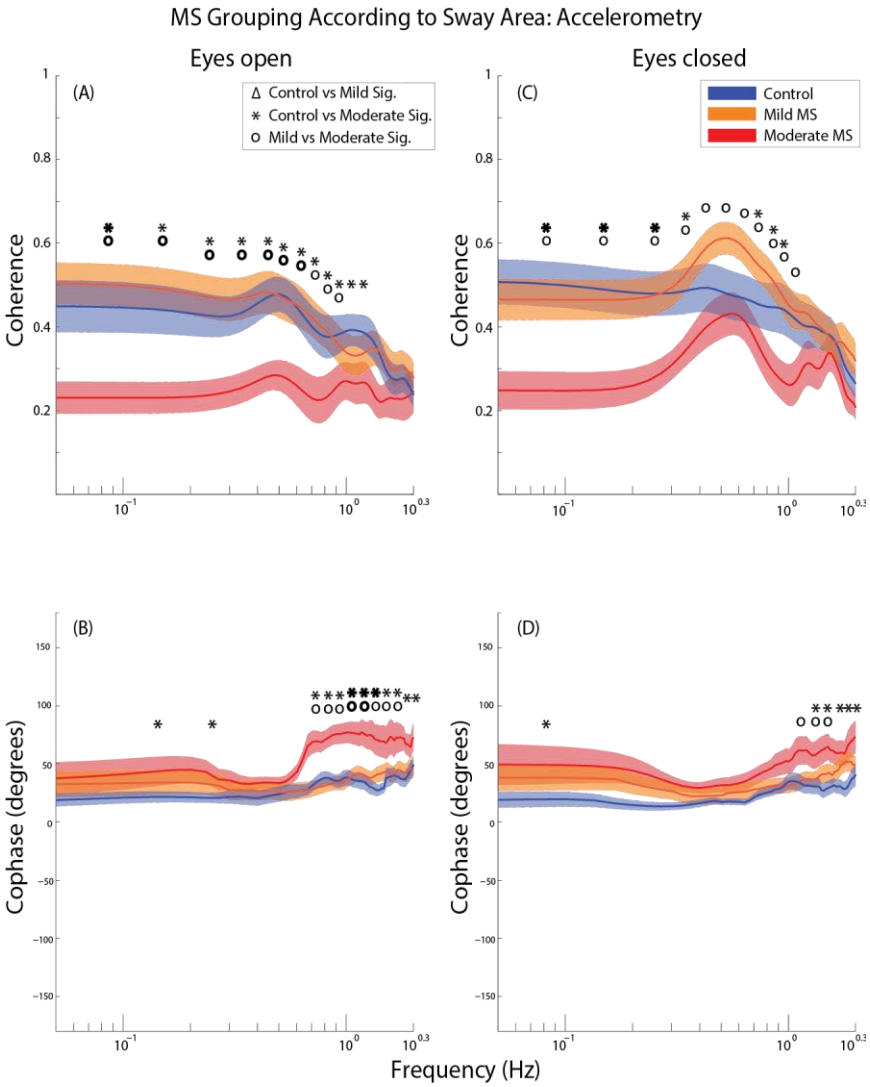

Figure 14. Coherence and cophase analysis using accelerometry data with anterior-posterior sway range group divisions. (A) Coherence in the eyes open condition. (B) Cophase in the eyes open condition. (C) Coherence in the eyes close condition. (D) Cophase in the eyes close condition. Solid lines indicate the mean of each subject group and shading illustrates the standard error of each group. Markers indicate uncorrected significance between groups and bold markers signify significant differences after the Bonferroni correction.

Table 2 Accelerometry: Between Group Significance: Coherence and Cophase in Eyes Open

		Control vs Mild			Control vs Moderate			Mild vs Moderate		
AP Sway Range		F Value	Raw Sig.	Bonf.	F Value	Raw Sig.	Bonf.	F Value	Raw Sig.	Bonf.
Coherence EO	Freq 1	0.71	0.400	1	**11.34**	**0.001**	**0.038**	**17.58**	**0**	**0.001**
Accelerometry	Freq 2	0.62	0.429	1	10.61	0.001	0.056	**16.28**	**0**	**0.003**
	Freq 3	0.54	0.462	1	8.74	0.003	0.153	**13.54**	**0**	**0.012**
	Freq 4	0.51	0.476	1	7.32	0.007	0.335	**11.57**	**0.001**	**0.034**
	Freq 5	0.28	0.592	1	8.14	0.004	0.213	**11.51**	**0.001**	**0.035**
	Freq 6	0.07	0.795	1	9.47	0.002	0.103	**11.37**	**0.001**	**0.037**
	Freq 7	0.17	0.684	1	8.60	0.003	0.165	**11.27**	**0.001**	**0.039**
	Freq 8	0.17	0.683	1	7.24	0.007	0.349	9.68	0.002	0.092
	Freq 9	0.03	0.868	1	5.94	0.015	0.718	6.94	0.009	0.411
	Freq 10	0.15	0.698	1	4.82	0.028	1	3.57	0.059	1
	Freq 11	0.42	0.518	1	4.30	0.039	1	2.33	0.127	1
	Freq 12	0.32	0.569	1	4.10	0.043	1	2.40	0.122	1
	Freq 13	0.06	0.811	1	3.46	0.063	1	2.82	0.093	1
	Freq 14	0.03	0.858	1	3.11	0.078	1	3.84	0.051	1
	Freq 15	0.26	0.609	1	2.00	0.158	1	3.62	0.057	1
	Freq 16	0.37	0.545	1	0.56	0.454	1	1.72	0.190	1
		Control vs Mild			Control vs Moderate			Mild vs Moderate		
AP Sway Range		F Value	Raw Sig.	Bonf.	F Value	Raw Sig.	Bonf.	F Value	Raw Sig.	Bonf.
Cophase EO	Freq 1	2.87	0.091	1	3.00	0.083	1	0.06	0.083	1
Accelerometry	Freq 2	2.55	0.111	1	3.91	0.048	1	0.33	0.135	1
	Freq 3	2.22	0.136	1	3.98	0.046	1	0.47	0.232	1
	Freq 4	1.04	0.308	1	2.24	0.135	1	0.37	0.135	1
	Freq 5	0.52	0.470	1	1.43	0.232	1	0.32	0.232	1
	Freq 6	0.09	0.766	1	5.19	0.023	1	0.83	0.361	1
	Freq 7	0.02	0.890	1	7.10	0.008	0.377	4.83	0.028	1
	Freq 8	0.03	0.857	1	8.38	0.004	0.187	8.29	0.004	0.196
	Freq 9	0.11	0.741	1	**12.39**	**0**	**0.022**	10.56	0.001	0.058
	Freq 10	0	0.986	1	**12.72**	**0**	**0.018**	**12.98**	**0**	**0.016**
	Freq 11	0.04	0.847	1	**11.22**	**0.001**	**0.041**	**11.97**	**0**	**0.027**
	Freq 12	0.39	0.534	1	9.19	0.003	0.121	8.13	0.005	0.214
	Freq 13	0.49	0.485	1	9.80	0.002	0.087	6.04	0.014	0.680
	Freq 14	0.90	0.343	1	7.59	0.006	0.287	5.44	0.020	0.954
	Freq 15	0.90	0.343	1	4.32	0.038	1	3.81	0.051	1
	Freq 16	0.20	0.657	1	4.32	0.038	1	2.95	0.086	1

Table 2: Between group statistics of coherence and cophase using accelerometry data with anterior-posterior sway range group divisions in the eyes open condition. Only notable values of significance reported. Bold values signify significant differences after the Bonferroni correction.

Table 3 Accelerometry: Between Group Significance: Coherence and Cophase in Eyes Closed

		Control vs Mild			Control vs Moderate			Mild vs Moderate		
AP Sway Range		F Value	Raw Sig.	Bonf.	F Value	Raw Sig.	Bonf.	F Value	Raw Sig.	Bonf.
Coherence EC	Freq 1	1.85	0.174	1	**17.24**	**0**	**0.002**	9.42	0.002	0.107
Accelerometry	Freq 2	1.24	0.266	1	**15.24**	**0**	**0.005**	9.24	0.002	0.117
	Freq 3	0.56	0.456	1	**11.82**	**0.001**	**0.030**	8.35	0.004	0.190
	Freq 4	0	0.989	1	7.46	0.006	0.309	8.13	0.005	0.214
	Freq 5	1.43	0.232	1	3.39	0.066	1	9.04	0.003	0.131
	Freq 6	3.28	0.071	1	1.11	0.291	1	7.58	0.006	0.290
	Freq 7	2.47	0.116	1	0.97	0.326	1	6.05	0.014	0.678
	Freq 8	1.20	0.274	1	2.75	0.097	1	7.43	0.007	0.314
	Freq 9	0.44	0.507	1	5.72	0.017	0.817	9.56	0.002	0.100
	Freq 10	0.01	0.931	1	7.68	0.006	0	8.76	0.003	0.152
	Freq 11	0	0.972	1	0.01	0.473	0.473	7.05	0.008	0.387
	Freq 12	0.04	0.833	1	3.65	0.056	1	4.75	0.030	1
	Freq 13	0.08	0.772	1	2.08	0.150	1	3.11	0.078	1
	Freq 14	0.01	0.906	1	2.03	0.154	1	2.53	0.112	1
	Freq 15	0	0.980	1	1.55	0.213	1	1.74	0.188	1
	Freq 16	0.02	0.899	1	1.14	0.286	1	0.98	0.321	1
		Control vs Mild			Control vs Moderate			Mild vs Moderate		
AP Sway Range		F Value	Raw Sig.	Bonf.	F Value	Raw Sig.	Bonf.	F Value	Raw Sig.	Bonf.
Cophase EC	Freq 1	1.40	0.238	1	4.49	0.034	1	1.26	0.263	1
Accelerometry	Freq 2	1.59	0.208	1	2.81	0.094	1	0.35	0.557	1
	Freq 3	1.96	0.162	1	2.77	0.097	1	0.20	0.654	1
	Freq 4	0.71	0.400	1	1.16	0.282	1	0.12	0.728	1
	Freq 5	0.21	0.647	1	0.65	0.419	1	0.18	0.674	1
	Freq 6	0.54	0.465	1	1.44	0.231	1	0.33	0.565	1
	Freq 7	0.84	0.359	1	2.22	0.136	1	0.51	0.478	1
	Freq 8	0.25	0.615	1	1.68	0.195	1	0.79	0.376	1
	Freq 9	0.03	0.859	1	1.98	0.160	1	1.69	0.194	1
	Freq 10	0.00	0.963	1	3.17	0.075	1	3.58	0.059	1
	Freq 11	0.15	0.697	1	2.86	0.091	1	4.47	0.035	1
	Freq 12	0.00	0.947	1	5.42	0.020	0.966	6.15	0.013	0.640
	Freq 13	0.03	0.852	1	4.64	0.032	1	4.28	0.039	1
	Freq 14	0.07	0.798	1	4.20	0.041	1	3.59	0.058	1
	Freq 15	1.08	0.300	1	6.74	0.010	0.460	3.06	0.081	1
	Freq 16	1.24	0.266	1	6.73	0.010	0.462	2.82	0.094	1

Table 3: Between group statistics of coherence and cophase using accelerometry data with anterior-posterior sway range group divisions in the eyes closed condition. Only notable values of significance reported. Bold values signify significant differences after the Bonferroni correction.

Kinematics

QS Eyes Open

The 3 groups showed coherence and cophase similar to accelerometry data, calculated from trunk and leg angle, during the eyes open condition (Table 4, Figure 15-A,B). However, moderate MS subjects showed lower coherence at low frequency with uncorrected significance compared to mild MS and control subjects (Figure 15-A).

QS Eyes Closed

Moderate MS subjects showed significantly lower coherence compared to mild MS and control subjects at the lower frequencies (F-values ranging from 10.87 to 23.61, and p-values ranging from 0.0010 to 0.0000 Bonferroni corrected),see Table 5 and Figure 15-C. Moreover, moderate MS subjects showed higher cophase (uncorrected significance) compared to control subjects at the very low and high frequencies, Figure 15.

The results from kinematic data in eyes open and eyes closed conditions show similar trends and shapes for both coherence and cophase. Coherence during eyes closed condition reflected greater differences between groups.

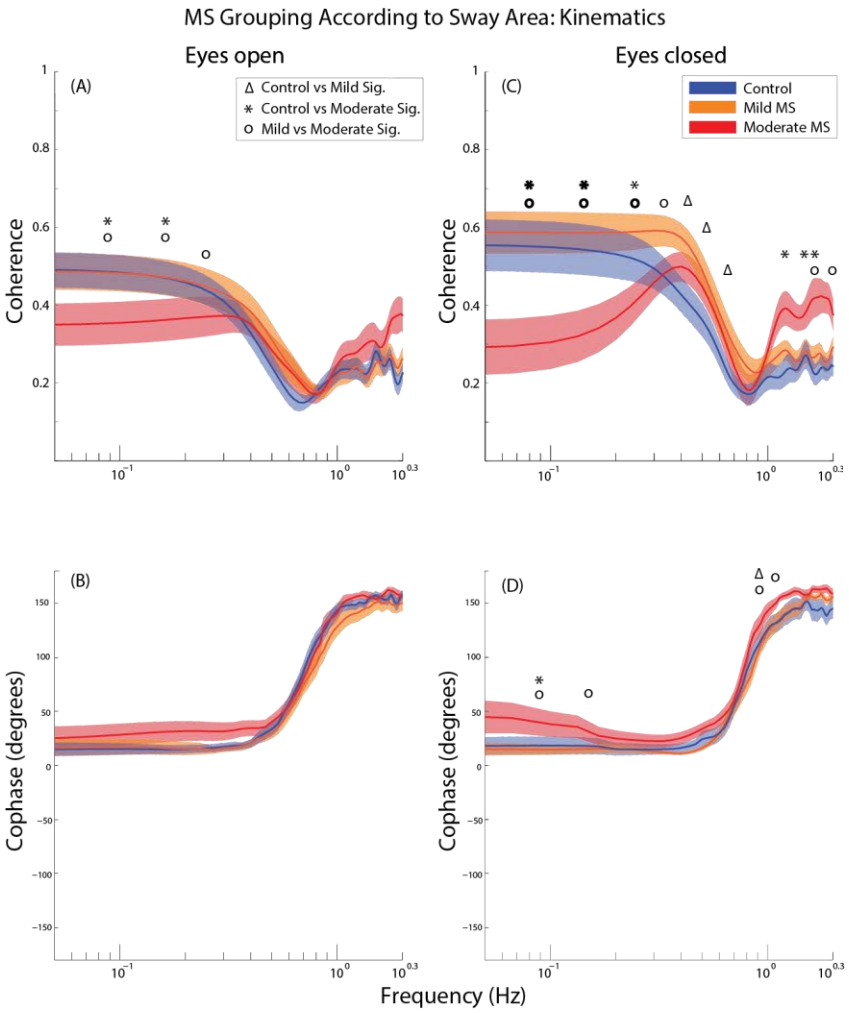

Figure 15. Coherence and cophase analysis using kinematic measures with anterior-posterior sway range group divisions. (A) Coherence in the eyes open condition. (B) Cophase in the eyes open condition. (C) Coherence in the eyes close condition. (D) Cophase in the eyes close condition. Solid lines indicate the mean of each subject group and shading illustrates the standard error of each group. Markers indicate uncorrected significance between groups and bold markers signify significant differences after the Bonferroni correction.

Table 4	Kinematics: Between Group Significance: Coherence and Cophase in Eyes Open									
		Control vs Mild			Control vs Moderate			Mild vs Moderate		
AP Sway Range		F Value	Raw Sig.	Bonf.	F Value	Raw Sig.	Bonf.	F Value	Raw Sig.	Bonf.
Coherence EO	Freq 1	0.16	0.692	1	7.44	0.007	0.313	9.85	0.002	0.084
Kinematics	Freq 2	0.23	0.635	1	5.24	0.022	1	7.62	0.006	0.282
	Freq 3	0.38	0.537	1	2.14	0.143	1	4.21	0.041	1
	Freq 4	1.22	0.269	1	0.09	0.766	1	1.70	0.193	1
	Freq 5	2.98	0.084	1	0.37	0.544	1	0.89	0.346	1
	Freq 6	3.37	0.067	1	0.93	0.334	1	0.45	0.500	1
	Freq 7	3.11	0.078	1	1.35	0.245	1	0.17	0.683	1
	Freq 8	1.00	0.317	1	0.25	0.617	1	0.16	0.693	1
	Freq 9	0.00	0.991	1	0.04	0.838	1	0.04	0.843	1
	Freq 10	0.01	0.926	1	0.00	0.963	1	0.02	0.895	1
	Freq 11	0.00	0.971	1	0.23	0.631	1	0.21	0.648	1
	Freq 12	0.01	0.910	1	0.52	0.469	1	0.40	0.525	1
	Freq 13	0.09	0.769	1	0.75	0.386	1	0.38	0.537	1
	Freq 14	0.01	0.942	1	1.99	0.159	1	1.88	0.170	1
	Freq 15	0.07	0.785	1	1.28	0.257	1	1.96	0.161	1
	Freq 16	0.07	0.799	1	0.19	0.662	1	0.46	0.499	1
		Control vs Mild			Control vs Moderate			Mild vs Moderate		
AP Sway Range		F Value	Raw Sig.	Bonf.	F Value	Raw Sig.	Bonf.	F Value	Raw Sig.	Bonf.
Cophase EO	Freq 1	0.06	0.810	1	1.05	0.307	1	0.68	0.410	1
Kinematics	Freq 2	0.08	0.778	1	2.28	0.131	1	1.65	0.200	1
	Freq 3	0.00	0.974	1	2.70	0.101	1	2.71	0.100	1
	Freq 4	0.00	0.966	1	2.31	0.129	1	2.52	0.113	1
	Freq 5	0.00	0.967	1	0.95	0.331	1	1.06	0.304	1
	Freq 6	0.11	0.743	1	0.23	0.630	1	0.62	0.431	1
	Freq 7	0.54	0.463	1	0.08	0.774	1	0.14	0.711	1
	Freq 8	1.98	0.159	1	0.62	0.430	1	0.22	0.641	1
	Freq 9	2.88	0.090	1	0.16	0.687	1	1.26	0.262	1
	Freq 10	1.31	0.252	1	0.00	0.984	1	1.12	0.291	1
	Freq 11	0.95	0.330	1	0.00	0.999	1	0.78	0.378	1
	Freq 12	0.18	0.670	1	0.30	0.581	1	0.90	0.344	1
	Freq 13	0.05	0.818	1	0.49	0.483	1	0.85	0.356	1
	Freq 14	0.01	0.931	1	0.45	0.504	1	0.36	0.546	1
	Freq 15	0.01	0.917	1	0.00	0.983	1	0.01	0.908	1
	Freq 16	0.02	0.878	1	0.05	0.825	1	0.13	0.716	1

Table 4: Between group statistics of coherence and cophase using kinematic data with anterior-posterior sway range group divisions in the eyes open condition. Only notable values of significance reported. Bold values signify significant differences after the Bonferroni correction.

Table 5 Kinematics: Between Group Significance: Coherence and Cophase in Eyes Close

		Control vs Mild			Control vs Moderate			Mild vs Moderate		
AP Sway Range		F Value	Raw Sig.	Bonf.	F Value	Raw Sig.	Bonf.	F Value	Raw Sig.	Bonf.
Coherence EC	Freq 1	0.35	0.557	1	**17.30**	**0**	**0.002**	**23.62**	**0**	**0.000**
Kinematics	Freq 2	0.59	0.443	1	**12.61**	**0**	**0.019**	**19.29**	**0**	**0.001**
	Freq 3	1.26	0.261	1	4.77	0.029	1	**10.87**	**0.001**	**0.049**
	Freq 4	3.20	0.074	1	0.28	0.598	1	4.77	0.029	1
	Freq 5	5.36	0.021	1	0.42	0.517	1	2.08	0.150	1
	Freq 6	4.87	0.028	1	0.98	0.322	1	0.98	0.323	1
	Freq 7	4.75	0.030	1	1.06	0.304	1	0.86	0.355	1
	Freq 8	2.53	0.112	1	0.04	0.849	1	1.58	0.209	1
	Freq 9	0.55	0.457	1	0.10	0.755	1	1.01	0.315	1
	Freq 10	0.09	0.764	1	0.09	0.761	1	0.00	0.968	1
	Freq 11	0.12	0.733	1	1.97	0.161	1	1.31	0.253	1
	Freq 12	0.54	0.464	1	6.22	0.013	0.617	3.69	0.055	1
	Freq 13	0.46	0.498	1	6.09	0.014	0.661	3.78	0.052	1
	Freq 14	0.12	0.724	1	4.98	0.026	1	3.98	0.046	1
	Freq 15	0.01	0.911	1	3.38	0.066	1	3.27	0.071	1
	Freq 16	0.0129	0.910	1	3.67	0.056	1	4.38	0.037	1

		Control vs Mild			Control vs Moderate			Mild vs Moderate		
AP Sway Range		F Value	Raw Sig.	Bonf.	F Value	Raw Sig.	Bonf.	F Value	Raw Sig.	Bonf.
Cophase EC	Freq 1	0.38	0.536	1	5.99	0.015	**0.699**	9.67	0.002	**0.092983**
Kinematics	Freq 2	0.29	0.593	1	2.33	0.128	1	4.30	0.038	1
	Freq 3	0.05	0.825	1	0.89	0.346	1	1.40	0.237	1
	Freq 4	0.32	0.569	1	0.43	0.510	1	1.45	0.228	1
	Freq 5	0.78	0.377	1	0.29	0.592	1	1.86	0.173	1
	Freq 6	0.74	0.390	1	0.63	0.428	1	2.59	0.108	1
	Freq 7	0.17	0.681	1	0.38	0.539	1	1.03	0.311	1
	Freq 8	1.52	0.217	1	0.04	0.851	1	1.75	0.186	1
	Freq 9	3.93	0.048	1	1.47	0.225	1	9.46	0.002	**0.104**
	Freq 10	0.72	0.397	1	2.22	0.137	1	5.40	0.020	**0.978**
	Freq 11	0.56	0.453	1	1.41	0.236	1	3.68	0.055	1
	Freq 12	0.49	0.485	1	1.35	0.245	1	3.41	0.065	1
	Freq 13	1.17	0.279	1	0.40	0.528	1	2.71	0.100	1
	Freq 14	1.53	0.216	1	0.32	0.569	1	2.97	0.085	1
	Freq 15	0.61	0.436	1	0.26	0.612	1	1.54	0.215	1
	Freq 16	0.07	0.784	1	0.00	0.967	1	0.09	0.769	1

Table 5: Between group statistics of coherence and cophase using kinematic data with anterior-posterior sway range group divisions in the eyes closed condition. Only notable values of significance reported. Bold values signify significant differences after the Bonferroni correction.

B. MS grouping according to Latency

Accelerometry

QS Eyes Open

The 3 groups showed similar coherence and cophase, calculated from ankle and trunk accelerations, (Figure 16-A,B). However, mild MS subjects showed higher cophase at low frequency with uncorrected significance compared control subjects (Figure 16-A).

QS Eyes Closed

As in the eyes open condition, the 3 groups showed similar coherence and cophase, calculated from ankle and trunk accelerations, (Figure 16-C,D). However, moderate MS subjects showed lower coherence at low frequency with uncorrected significance compared control subjects (Figure 16-C).

Although no significance was found, the coherence between ankle and trunk acceleration in eyes open and eyes closed conditions displayed similar visual trends such as constant coherence at the lowest frequencies followed by an increase causing a peak near 0.6Hz and then a decrease at higher frequencies.

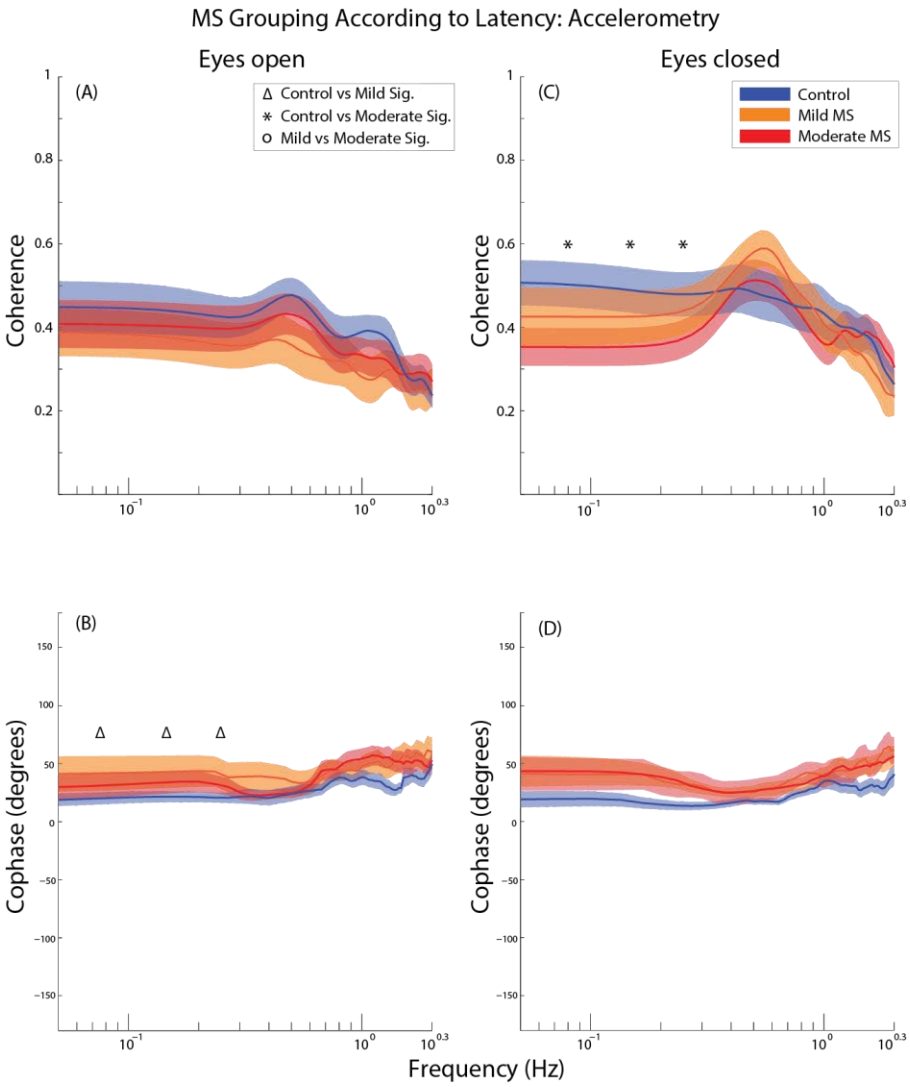

Figure 16. Coherence and cophase analysis using accelerometry data with latency group divisions. (A) Coherence in the eyes open condition. (B) Cophase in the eyes open condition. (C) Coherence in the eyes close condition. (D) Cophase in the eyes close condition. Solid lines indicate the mean of each subject group and shading illustrates the standard error of each group. Markers indicate uncorrected significance between groups and bold markers signify significant differences after the Bonferroni correction.

Kinematics

QS Eyes Open

In keeping with accelerometry results, no significant groups differences was observed in coherence and cophase calculated from trunk and leg angle (Figure 17-A,B). However, mild MS subjects showed significantly higher cophase compared to moderate MS subjects only at one frequency (Figure 17-B).

Moreover, moderate MS subjects showed higher coherence at middle frequencies compared to mild MS and control subjects with uncorrected significance (Figure 17-A).

QS Eyes Closed

Similarly to the eyes open conditions, no significant groups difference was observed in coherence and cophase during the eyes closed condition (Figure 17-C,D).
However, the moderate MS subjects showed higher coherence at middle frequencies compared to mild MS and control subjects with uncorrected significance (Figure 17-C).

Despite the lack of significance between groups, patients in both conditions displayed similar coherence and cophase patterns across all analyzed frequencies, which is apparent in Figure 17.

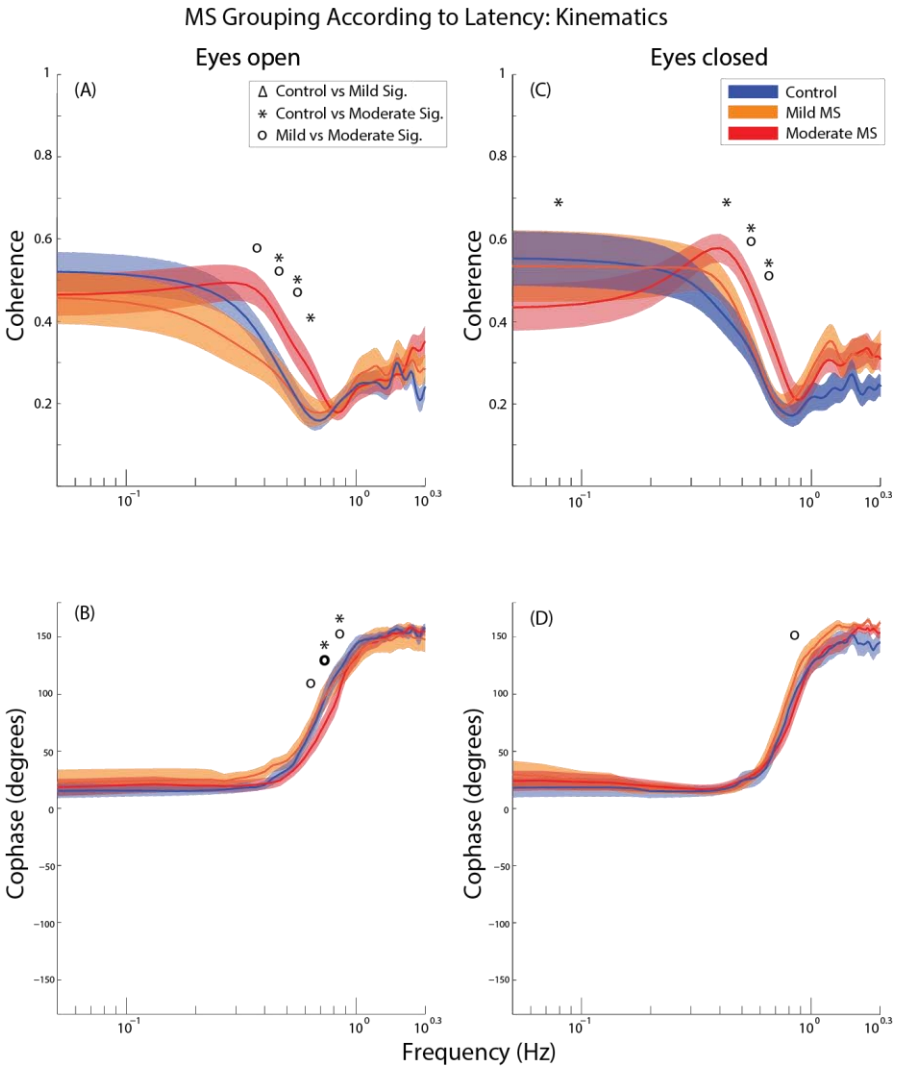

Figure 17. Coherence and cophase analysis using kinematic data with latency group divisions.
(A) Coherence in the eyes open condition.
(B) Cophase in the eyes open condition.
(C) Coherence in the eyes close condition.
(D) Cophase in the eyes close condition.
Solid lines indicate the mean of each subject group and shading illustrates the standard error of each group. Markers indicate uncorrected significance between groups and bold markers signify significant differences after the Bonferroni correction.

C. MS grouping according to walking speed measured by the 25ft walk test

Accelerometry

QS Eyes Open

The 3 groups showed similar coherence and cophase, calculated from leg and trunk accelerations, (Figure 18-A,B). However, mild MS subjects showed higher cophase at low frequency with uncorrected significance compared control subjects, and moderate MS showed higher cophase at frequencies above 1Hz, uncorrected significance (Figure 18-B).

QS Eyes Closed

As in the eyes open condition, the 3 groups showed similar coherence and cophase, calculated from ankle and trunk accelerations, (Figure 18-C,D). However, moderate MS subjects showed lower coherence at low frequency with uncorrected significance compared control subjects (Figure 18-C) together with higher cophase compared to control subjects (Figure 18-D).

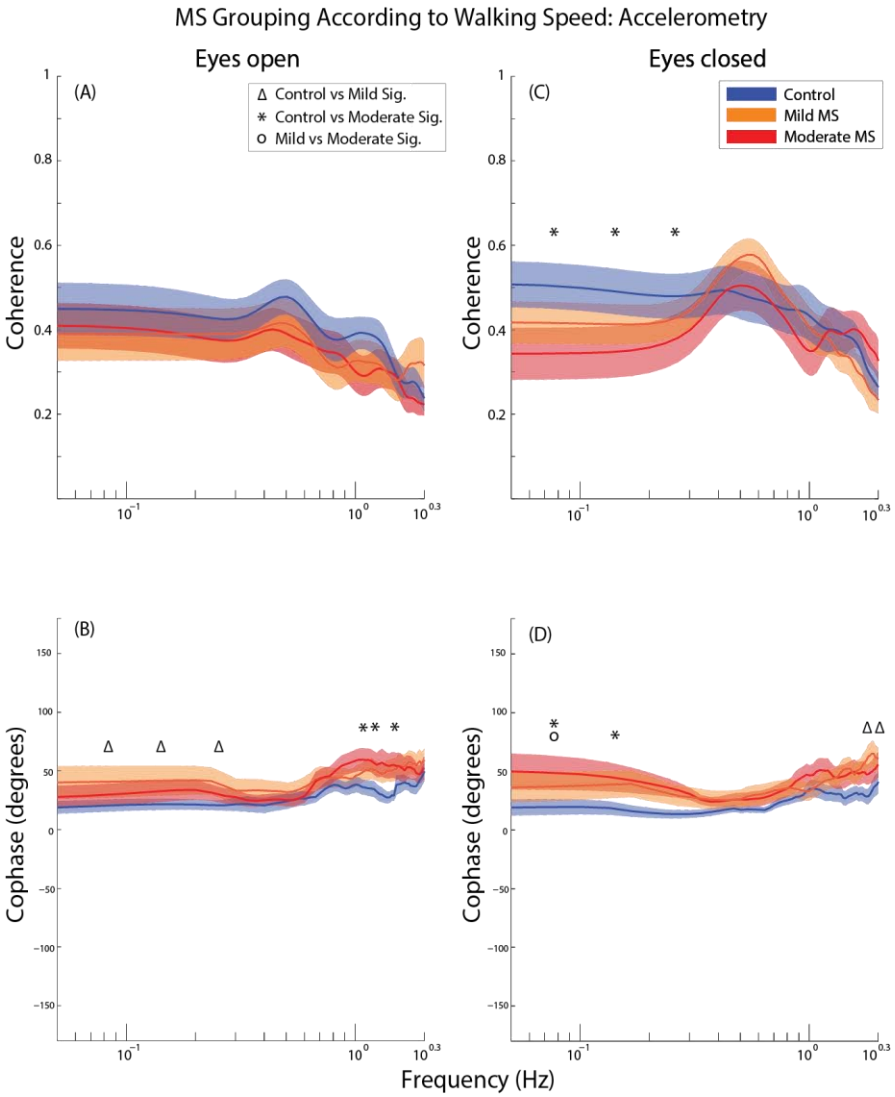

Figure 18. Coherence and cophase analysis using accelerometry data with walking speed group divisions. (A) Coherence in the eyes open condition. (B) Cophase in the eyes open condition. (C) Coherence in the eyes close condition. (D) Cophase in the eyes close condition. Solid lines indicate the mean of each subject group and shading illustrates the standard error of each group. Markers indicate uncorrected significance between groups and bold markers signify significant differences after the Bonferroni correction.

Kinematics

<u>QS Eyes Open</u>

In keeping with accelerometry results, no significant groups differences was observed in coherence and cophase calculated from trunk and leg angle (Figure 19-A,B). However, moderate MS subjects showed higher coherence at middle frequencies compared to mild MS and control subjects (Figure 19-A), together with lower cophase at the middle frequencies compared to mild MS and control subjects (Figure 19-B).

QS Eyes Closed

Similarly to the eyes open conditions, no significant groups difference was observed in coherence and cophase during the eyes closed condition (Figure 19-C,D).

However, the moderate MS subjects showed lower coherence at the low frequencies compared to mild MS and control subjects with uncorrected significance (Figure 19-C). In addition, the moderate MS subjects showed higher coherence at middle frequencies compared to mild MS and control subjects with uncorrected significance (Figure 19-C) together with lower cophase compared to mild MS and control subjects (Figure 19-D).

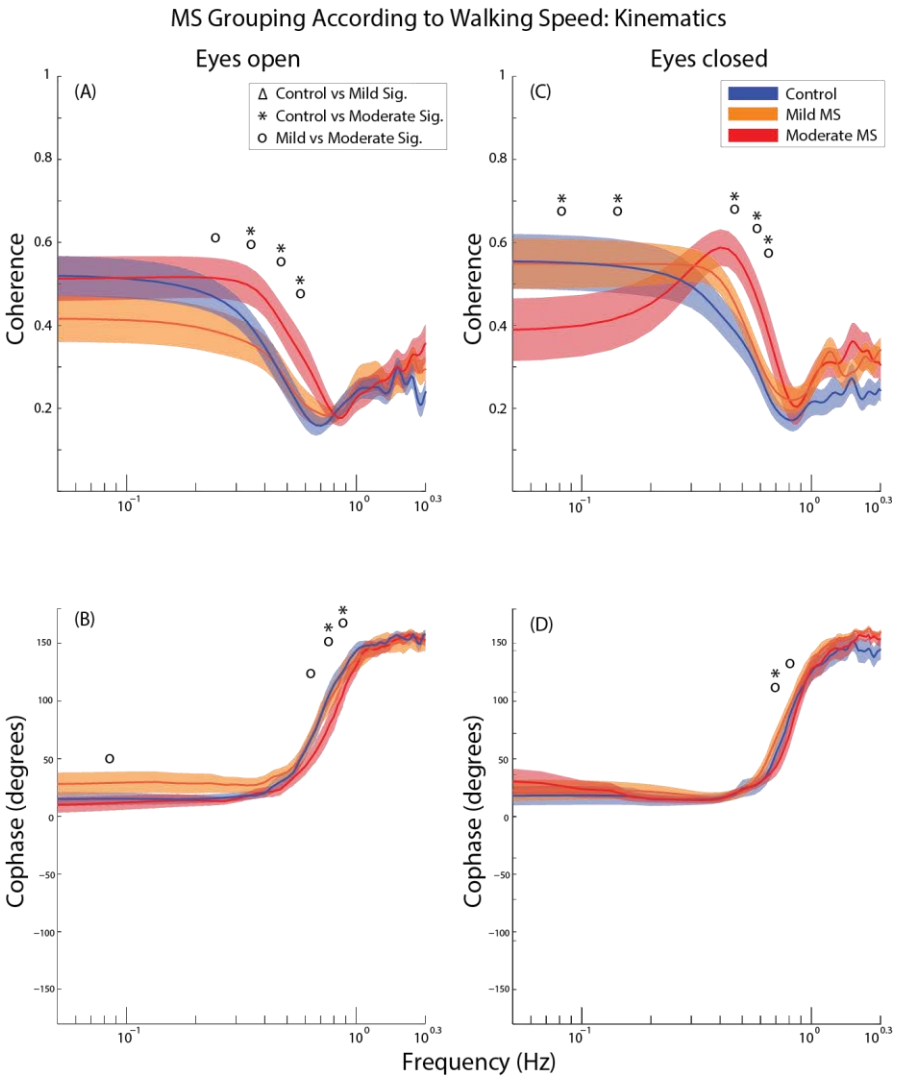

Figure 19. Coherence and cophase analysis using kinematic data with walking speed group divisions. (A) Coherence in the eyes open condition. (B) Cophase in the eyes open condition. (C) Coherence in the eyes close condition. (D) Cophase in the eyes close condition. Solid lines indicate the mean of each subject group and shading illustrates the standard error of each group. Markers indicate uncorrected significance between groups and bold markers signify significant differences after the Bonferroni correction.

2. MS and control subjects changed strategy at similar frequencies (identified by cophase crossing at 90°) and at similar coherence values, both in QS eyes open and closed.

No statistical differences between groups were found in either frequency at which the cophase crosses 90° or for the value of the coherence at the crossing. Similar results were found for the different criteria of separating MS in mild and moderate; and also when considering MS subjects as one group, see Table 6 below. Refer to figure 20 for a visual representation of values being used for this analysis.

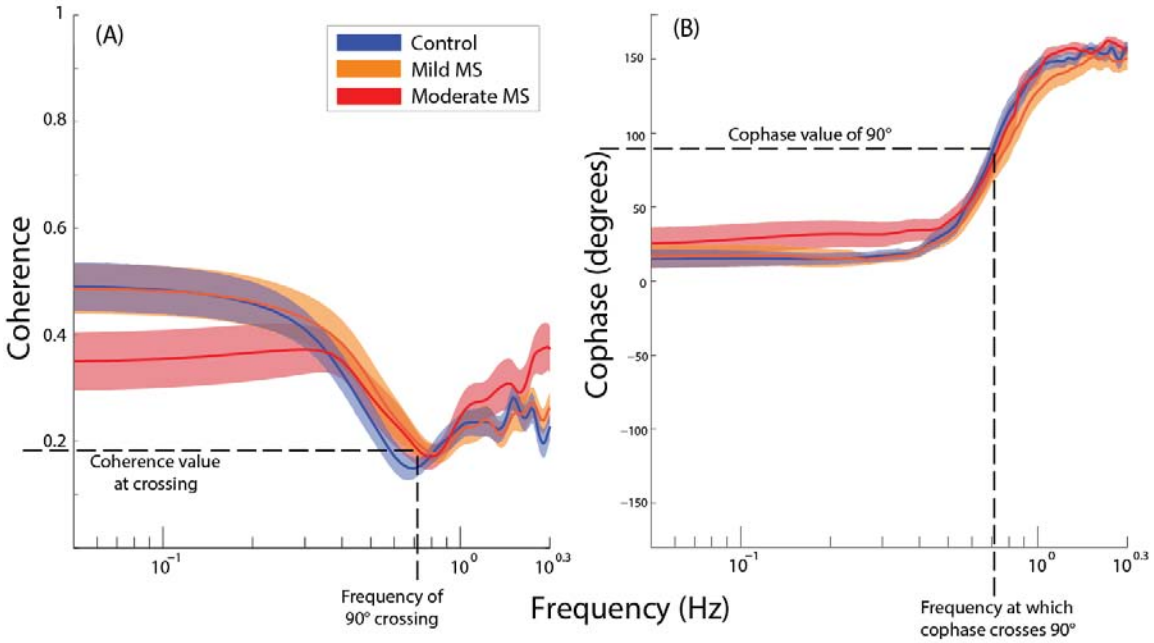

Figure 20: A visual representation of the frequency at which the cophase cross 90° and the coherence value at that frequency for the Moderate MS group. (B) First the 90° crossing is determined from the cophase and the frequency of that crossing is recorded. The coherence at that frequency is then obtained (A).

Table 6 Significant Differences at Cophase 90° Between Groups				
Frequency of 90° Crossing	Sensor	Condition	F Value	Between Group Sig.
MS versus Control	Kinematics	EO	0.32	0.575
		EC	0.13	0.716
Coherence Value at Crossing	Sensor	Condition	F Value	Between Group Sig.
MS versus Control	Kinematics	EO	0.04	0.852
		EC	0.08	0.786

Table 6: MS versus control statistics of the frequency at which cophase crosses 90° and the value of coherence at that frequency in kinematic data. Statistics for all three group separations and both eyes open and eyes close conditions included.

Table 7 Significant Differences at Cophase 90° Between Groups				
Frequency of 90° Crossing	Sensor	Condition	F Value	Between Group Sig.
Latency	Kinematics	EO	1.19	0.314
		EC	0.40	0.671
Walk	Kinematics	EO	1.30	0.281
		EC	2.21	0.121
Sway Area EC	Kinematics	EO	0.21	0.814
		EC	0.51	0.604
Coherence Value at Crossing	Sensor	Condition	F Value	Between Group Sig.
Latency	Kinematics	EO	0.23	0.800
		EC	0.05	0.951
Walk	Kinematics	EO	0.03	0.979
		EC	0.62	0.540
Sway Range EC	Kinematics	EO	0.23	0.799
		EC	0.09	0.910

Table 7: Mild versus moderate versus control statistics of the frequency at which cophase crosses 90° and the value of coherence at that frequency in kinematic data. Statistics for all three group separations and both eyes open and eyes close conditions included.

3. Mild MS and control subjects changed strategy at higher frequencies (identified by cophase crossing at 90°) during QS eyes closed compared to eyes open, while moderate MS did not, in all three group classifications.

When comparing the frequency at which the cophase crosses 90° between the eyes open and the eyes closed condition, significant differences were found. The mild MS and control subjects changed phase coordination between upper and lower body at higher frequencies during eyes closed condition compared to eyes open (see Table 8 and 9).

Table 8 Between Condition Significance: Cophase 90° Crossing

Variable	Sensor	Condition	F Value	Between Group Sig.
Frequency of 90° Crossing	Kinematics	EO vs EC	**5.07**	**0.038**
Coherence Value at 90° Crossing	Kinematics	EO vs EC	1.22	0.285

Table 8: Control group statistics of the frequency at which cophase crosses 90° and the value of coherence at that frequency in kinematic data. Statistics for all three group separations and both eyes open and eyes close conditions included. Bold values signify significant differences after the Bonferroni correction.

Table 9 Significant Differences at Cophase 90° Between Conditions					
Frequency of 90° Crossing	Sensor	Condition	Group	F Value	Between Condition Sig.
Latency	Kinematics	EOvsEC	MS	**6.63**	**0.016**
			Mild	**6.39**	**0.028**
			Moderate	1.87	0.190
25ft Walk	Kinematics	EOvsEC	MS	**6.63**	**0.016**
			Mild	**5.10**	**0.039**
			Moderate	1.77	0.208
Sway Area EC	Kinematics	EOvsEC	MS	**6.63**	**0.016**
			Mild	**6.18**	**0.024**
			Moderate	1.49	0.248
Coherence Value 90° Crossing	Sensor	Condition	Group	F Value	Between Condition Sig.
Latency	Kinematics	EOvsEC	MS	0.01	0.923
			Mild	0.21	0.659
			Moderate	0.133	0.720
25ft Walk	Kinematics	EOvsEC	MS	0.01	0.923
			Mild	0.21	0.654
			Moderate	1.22	0.285
Sway Area EC	Kinematics	EOvsEC	MS	0.01	0.923
			Mild	0.03	0.878
			Moderate	1.22	0.285

Table 9: MS, mild, and moderate group statistics of the frequency at which cophase crosses 90° and the value of coherence at that frequency in kinematic data. Statistics for all three group separations and both eyes open and eyes close conditions included. Bold values signify significant differences after the Bonferroni correction.

4. MS and control subjects reached the minimum in coherence at similar frequencies and at a similar cophase value

There was no significant difference between the MS and control subjects when considering the frequency at which the minimum coherence occurs nor at the value of the cophase at that frequency.

However, for the separation according to latencies, moderate MS subjects showed a minimum in coherence at higher frequencies compared to mild MS subjects (p=0.038)

only in the eyes closed condition. Moreover, mild MS subjects showed a lower cophase value associated to the minimum coherence compared to control subjects (p=0.029). For the separation according to sway range, moderate MS subjects showed a higher value of cophase associated to the minimum in coherence compared to mild MS and control subjects (p=0.025 and p=0.041 respectively). Refer to figure 21 for a visual representation of values being used for this analysis.

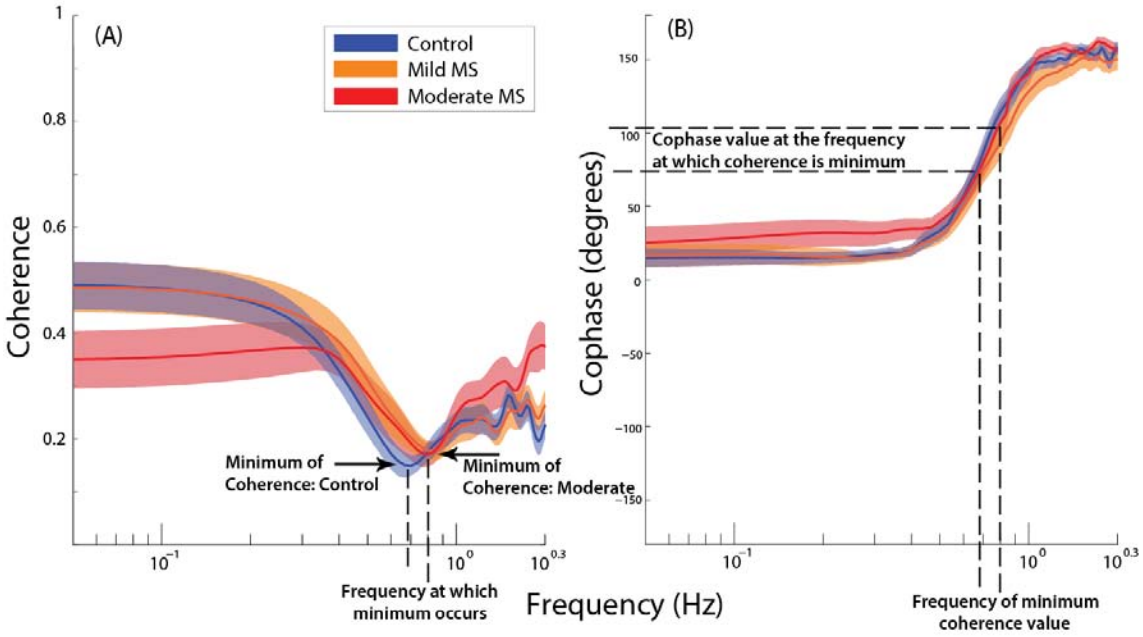

Figure 21: A visual representation of the frequency value of the minimum coherence and the cophase value at that frequency for the Moderate MS and Control groups. (A) The minimum value of coherence is found and the frequency is then the frequency of the occurrence is determined. (B) The cophase value at that frequency is then recorded.

Table 10 Between Group Significance: Minimum Value of Coherence				
Frequency of Minimum Value	Sensor	Condition	F Value	Between Group Sig.
Latency	Accelerometry	EO	0.23	0.636
		EC	0.18	0.673
	Kinematics	EO	0.11	0.745
		EC	0.02	0.886
Cophase Value at Minimum Frequency	Sensor	Condition	F Value	Between Group Sig.
Latency	Accelerometry	EO	2.07	0.156
		EC	1.08	0.303
	Kinematics	EO	0.53	0.468
		EC	3.01	0.088

Table 10: MS versus control group statistics of the frequency at which coherence is minimum and the value of cophase at that frequency in accelerometry and kinematic data. Statistics for all three group separations and both eyes open and eyes close conditions included.

Table 11 Between Group Significance: Minimum Value of Coherence							
Frequency of Minimum Value	Sensor	Condition	F Value	Between Group Sig.	Bonf. Control vs. Mild	Bonf. Control vs. Moderate	Bonf. Mild vs. Moderate
Latency	Accelerometry	EO	0.622	0.541			
		EC	0.377	0.688			
	Kinematics	EO	1.553	0.221	0.339	0.991	0.038
		EC	3.342	0.043			
Walk	Accelerometry	EO	0.147	0.864			
		EC	0.116	0.517			
	Kinematics	EO	1.142	0.327			
		EC	1.519	0.228			
Sway Range EC	Accelerometry	EO	1.015	0.369			
		EC	2.053	0.138			
	Kinematics	EO	0.199	0.820			
		EC	0.721	0.491			
Cophase Value at Min. Frequency	Sensor	Condition	F Value	Between Group Sig.	Bonf. Control vs. Mild	Bonf. Control vs. Moderate	Bonf. Mild vs. Moderate
Latency	Accelerometry	EO	1.020	0.368			
		EC	0.722	0.490			
	Kinematics	EO	0.527	0.593	0.029	1	0.115
		EC	3.865	0.027			
Walk	Accelerometry	EO	1.028	0.365			
		EC	0.538	0.589			
	Kinematics	EO	0.398	0.674			
		EC	1.907	0.159			
Sway Range EC	Accelerometry	EO	4.384	0.017	1	0.025	0.041
		EC	1.656	0.201			
	Kinematics	EO	0.599	0.553			
		EC	2.261	0.114			

Table 11: Mild versus moderate versus control group statistics of the frequency at which coherence is minimum and the value of cophase at that frequency in accelerometry and kinematic data. Only Bonferroni corrected values of significance reported for all three group separations and both eyes open and eyes close conditions included.

5. Overall Frequency Analysis

In all but two cases (coherence and cophase calculated from kinematics data in the MS group during eyes closed QS, and coherence and cophase calculated from kinematics data in the moderate MS group during eyes closed separated by latencies), significant difference in cophase value between adjacent frequencies were found at frequencies following those of coherence changes.

Control Subjects

A significant changes in coherence values at frequency intervals of 0.43Hz to 0.53Hz, of 0.53Hz to 0.63Hz ($p < 0.02$) together with a significant change in cophase at frequency intervals of 0.53Hz to 0.63Hz ($p \sim 0$) were found in control subjects during the eyes open condition, only for kinematics based measures. Similarly, in eyes closed condition, significance was found between frequencies 0.53Hz and 0.63Hz in coherence ($p < 0.006$) and 0.83Hz and 0.93Hz in the cophase ($p< 0.009$).

Table 12 Within-Group Frequency Analysis: Control				
25ft Walk				
Sensor	Condition	Frequency	Coherence Sig.	Cophase Sig.
Accelerometry	EC	1 to 2	1	1
		2 to 3	1	1
		3 to 4	1	1
		4 to 5	1	1
		5 to 6	1	1
		6 to 7	1	1
		7 to 8	1	1
		8 to 9	1	1
		9 to 10	0.594	1
Accelerometry	EO	1 to 2	1	1
		2 to 3	1	1
		3 to 4	1	0.787
		4 to 5	1	1
		5 to 6	0.996	1
		6 to 7	1	1
		7 to 8	1	1
		8 to 9	1	1
		9 to 10	1	1
Kinematics	EC	1 to 2	1	1
		2 to 3	0.725	1
		3 to 4	**0.006**	1
		4 to 5	0.453	1
		5 to 6	1	1
		6 to 7	1	0.009
		7 to 8	1	1
		8 to 9	1	1
		9 to 10	1	1
Kinematics	EO	1 to 2	0.921	1
		2 to 3	0.057	1
		3 to 4	**0.019**	0.103
		4 to 5	0.633	**0**
		5 to 6	1	1
		6 to 7	1	1
		7 to 8	1	1
		8 to 9	1	1
		9 to 10	1	1

Table 12: Control group statistics of within-group frequency analysis in accelerometry and kinematic data. All statistical values for two group separations and both eyes open and eyes close conditions included. Bold values signify significant differences after the Bonferroni correction.

Overall MS Subjects

When all MS subjects were considered together, within-group significant differences were found in adjacent frequency values of cophase and coherence. In accelerometry measures of eyes

closed QS, significance was found between frequencies 0.6Hz-0.7Hz ($p < 0.04$). In kinematics measures of eyes closed, differences were found in coherence between frequencies 0.43Hz-0.53Hz, 0.53Hz-0.63Hz, and 0.63Hz-0.73Hz, ($p < 0.008$) as well as cophase differences between frequencies 0.43Hz-0.53Hz and 0.63Hz-0.73Hz ($p < 0.005$). In kinematics eyes open trials, only a difference in coherence was observed between frequencies 0.43Hz-0.53Hz ($p < 0.008$).

Table 13 Within-Group Frequency Analysis: MS				
25ft Walk				
Sensor	Condition	Frequency	Coherence Sig.	Cophase Sig.
Accelerometry	EC	1 to 2	0.173	1
		2 to 3	0.071	1
		3 to 4	0.567	1
		4 to 5	1	1
		5 to 6	**0.037**	1
		6 to 7	0.055	1
		7 to 8	0.162	1
		8 to 9	1	1
		9 to 10	1	1
Accelerometry	EO	1 to 2	1	1
		2 to 3	1	1
		3 to 4	1	0.104
		4 to 5	1	1
		5 to 6	0.800	1
		6 to 7	1	1
		7 to 8	1	1
		8 to 9	1	1
		9 to 10	1	1
Kinematics	EC	1 to 2	1	1
		2 to 3	1	1
		3 to 4	**0**	**0.005**
		4 to 5	**0**	0.747
		5 to 6	**0.008**	**0**
		6 to 7	1	0.604
		7 to 8	1	1
		8 to 9	0.083	1
		9 to 10	0.561	1
Kinematics	EO	1 to 2	1	1
		2 to 3	0.254	0.594
		3 to 4	**0.001**	0.257
		4 to 5	**0.006**	0.643
		5 to 6	1	1
		6 to 7	1	0.437
		7 to 8	1	1
		8 to 9	1	1
		9 to 10	1	1

Table 13: MS group statistics of within-group frequency analysis in accelerometry and kinematic data. All statistical values for two group separations and both eyes open and eyes close conditions included. Bold values signify significant differences after the Bonferroni correction.

Mild MS Subjects

In mild MS patients, separated both by walking speed and latency, a significant difference was found in coherence between 0.43Hz and 0.53Hz as well as 0.53Hz and 0.63Hz ($p < 0.008$) using the walking speed division and 0.43Hz and 0.53Hz with the latency division ($p < 0.04$), all during eyes closed QS. Also, a significant change in cophase values between 0.63Hz and 0.73Hz was found ($p < 0.009$ and $p < 0.04$ for walking and latency divisions respectively).

Table 14 Within-Group Frequency Analysis: Mild

25ft Walk					Latency				
Sensor	Condition	Frequency	Coherence Sig.	Cophase Sig.	Sensor	Condition	Frequency	Coherence Sig.	Cophase Sig.
Accelerometry	EC	1 to 2	1	1	Accelerometry	EC	1 to 2	1	1
		2 to 3	0.240	1			2 to 3	0.240	1
		3 to 4	1	1			3 to 4	1	1
		4 to 5	1	1			4 to 5	1	1
		5 to 6	0.724	1			5 to 6	0.724	1
		6 to 7	0.412	1			6 to 7	0.412	1
		7 to 8	1	1			7 to 8	1	1
		8 to 9	1	1			8 to 9	1	1
		9 to 10	1	1			9 to 10	1	1
Accelerometry	EO	1 to 2	1	1	Accelerometry	EO	1 to 2	1	1
		2 to 3	1	1			2 to 3	1	1
		3 to 4	1	1			3 to 4	1	1
		4 to 5	1	1			4 to 5	1	1
		5 to 6	1	1			5 to 6	1	1
		6 to 7	1	1			6 to 7	1	0.979
		7 to 8	1	1			7 to 8	1	1
		8 to 9	1	1			8 to 9	1	1
		9 to 10	1	1			9 to 10	1	1
Kinematics	EC	1 to 2	1	1	Kinematics	EC	1 to 2	1	1
		2 to 3	1	1			2 to 3	1	1
		3 to 4	**0.006**	1			3 to 4	0.055	1
		4 to 5	**0.008**	1			4 to 5	**0.033**	1
		5 to 6	1	0.288			5 to 6	1	**0.043**
		6 to 7	1	0.604			6 to 7	1	1
		7 to 8	1	**0.009**			7 to 8	1	1
		8 to 9	1	1			8 to 9	1	1
		9 to 10	0.056	1			9 to 10	0.706	1
Kinematics	EO	1 to 2	1	1	Kinematics	EO	1 to 2	1	1
		2 to 3	1	1			2 to 3	1	1
		3 to 4	0.103	1			3 to 4	0.358	1
		4 to 5	0.255	0.740			4 to 5	1	1
		5 to 6	1	1			5 to 6	1	1
		6 to 7	1	1			6 to 7	1	1
		7 to 8	1	1			7 to 8	1	1
		8 to 9	1	1			8 to 9	1	1
		9 to 10	1	1			9 to 10	1	1

Table 14: Mild group statistics of within-group frequency analysis in accelerometry and kinematic data. All statistical values for two group separations and both eyes open and eyes close conditions included. Bold values signify significant differences after the Bonferroni correction.

Moderate MS Subjects

Similarly, in eyes close trials, coherence values of moderate patients were significantly different from one another at frequencies 0.53Hz to 0.63Hz and 0.63Hz to 0.73Hz, and a cophase difference between the latter frequency range as well. Moderate subjects classified by latency also included coherence and cophase differences between 0.43Hz and 0.53Hz. In the latency division, eyes open trials measured by kinematics found a significant difference between frequencies 0.43Hz and 0.53Hz in coherence and 0.53Hz to 0.63Hz in cophase.

Table 15 Within-Group Frequency Analysis: Moderate

25ft Walk					Latency				
Sensor	Condition	Frequency	Coherence Sig.	Cophase Sig.	Sensor	Condition	Frequency	Coherence Sig.	Cophase Sig.
Accelerometry	EC	1 to 2	1	1	Accelerometry	EC	1 to 2	1	1
		2 to 3	1	1			2 to 3	1	1
		3 to 4	1	1			3 to 4	1	1
		4 to 5	1	1			4 to 5	1	1
		5 to 6	0.948	1			5 to 6	0.264	1
		6 to 7	1	1			6 to 7	1	1
		7 to 8	1	1			7 to 8	1	1
		8 to 9	1	1			8 to 9	1	1
		9 to 10	1	1			9 to 10	1	1
Accelerometry	EO	1 to 2	1	1	Accelerometry	EO	1 to 2	1	1
		2 to 3	1	1			2 to 3	1	1
		3 to 4	1	1			3 to 4	1	1
		4 to 5	1	1			4 to 5	1	1
		5 to 6	1	1			5 to 6	1	1
		6 to 7	1	0.325			6 to 7	1	1
		7 to 8	1	1			7 to 8	1	1
		8 to 9	1	1			8 to 9	1	1
		9 to 10	1	1			9 to 10	1	1
Kinematics	EC	1 to 2	0.091	1	Kinematics	EC	1 to 2	0.487	1
		2 to 3	1	1			2 to 3	1	1
		3 to 4	0.351	0.077			3 to 4	**0.037**	**0.011**
		4 to 5	**0.010**	1			4 to 5	**0.002**	1
		5 to 6	**0.002**	1			5 to 6	**0.001**	**0.007**
		6 to 7	0.622	**0.001**			6 to 7	0.189	1
		7 to 8	1	1			7 to 8	1	1
		8 to 9	0.959	1			8 to 9	0.460	1
		9 to 10	1	1			9 to 10	1	1
Kinematics	EO	1 to 2	1	0.950	Kinematics	EO	1 to 2	1	1
		2 to 3	0.539	1			2 to 3	0.800	1
		3 to 4	0.144	1			3 to 4	**0.047**	1
		4 to 5	0.715	1			4 to 5	0.128	0.099
		5 to 6	1	1			5 to 6	1	1
		6 to 7	1	1			6 to 7	1	0.226
		7 to 8	1	1			7 to 8	1	1
		8 to 9	1	1			8 to 9	1	1
		9 to 10	1	1			9 to 10	1	1

Table 15: Moderate group statistics of within-group frequency analysis in accelerometry and kinematic data. All statistical values for two group separations and both eyes open and eyes close conditions included. Bold values signify significant differences after the Bonferroni correction.

Chapter 4 Discussion

1. Balance Strategies in Subjects with Multiple Sclerosis

The primary aim of this study was to determine whether subjects with MS use a different balance strategy compared to control subjects, using coherence and cophase analysis of trunk and leg segment accelerometry and kinematics. Our results showed that MS subjects with larger than normal postural sway range had significantly lower coherence at low frequencies compared to both control subjects and MS subjects with normal sway range. Furthermore, MS subjects with large sway showed greater anti-phase motion between the leg and the trunk at 0.05Hz than the control group. These results indicate that MS patients with large sway use a less coordinated, more hip strategy than healthy control subjects to maintain their balance during quiet standing. However, MS patients with normal sway area showed similar postural strategies as control subjects, suggesting that sway area, and not MS, alone, was responsible for abnormal postural strategies. MS subjects with largest sway area with eyes closed can be considered those with the most abnormal balance control when somatosensory information is critical because of the loss of vision.

Coherence between the trunk and shank motions during sway was more abnormal than the cophase in the MS compared to the control group. The primary trend of interest is the lower coherence of moderate MS subjects compared to control subjects, especially

at the lower frequencies, where significance was reached (F-values ranging from 11.81 to 17.30 and p-values ranged from 0.0016 to 0.02). This low coherence suggests that the movements of the trunk and leg are not strongly related. This is not surprising, considering the potential involvement of slowed somatosensory conduction in many patients with MS. In essence, patients are receiving sensory feedback from their feet later than healthy individuals, which results not only in inaccurate postural information, but also delayed balance corrections. Since the brain is using delayed somatosensory information for balance, it is not surprising that coordination between the upper and lower body is impaired. This difference between groups is potentially more apparent at the lowest frequencies because low frequencies have been shown to be dominated by the ankle strategy, which is characterized by high coherence and in-phase motion of the trunk and leg.[65]

The moderate MS subjects were found to have more anti-phase motion between the upper the lower body than control subjects at 0.05Hz. High cophase, or anti-phase motion, is associated with the hip strategy, which suggests that moderate, but not mild, patients with MS are attempting to use more hip strategy due to delayed somatosensory information. The increased reliance on hip strategy could be beneficial to subjects who have delayed somatosensory inputs because the CoM is moved faster with the hip strategy than the ankle strategy and because the distance from the brain to and from the hip muscles is shorter than to the ankle muscles.

Another interesting observation involves the peak of coherence around 0.63Hz. The mild and moderate MS groups both have a sharp increase in coherence, while as the control group had a nearly indistinguishable peak in the eyes closed condition. This increased coherence is accompanied by a near zero cophase, suggesting a stronger dependence on ankle strategy around this frequency. Since this trend only occurs in MS groups, it is possible that this is an adaptive mechanism used to manage other deficiencies, such as weakness, spasticity and/or somatosensory loss.

Three distinct classifications of MS severity were used for analysis because no single measure is commonly agreed upon as the best measure of severity. The use of postural reaction latencies in response to a platform perturbations was chosen because it reflects slowed propriospinal conduction from leg muscles up to the cortex.[11] Walking speed measured by the 25-foot walk was selected because it is the most commonly used gain test in clinical practice. Anterior-posterior sway range was another relevant criterion because of the strong relationship between balance, falls and sway area, as well as prior research demonstrating increased sway area in subjects with MS.[2][3] Neither walking speed nor latency assortments, however, were able to distinguish significant differences in coherence between any pair of groups. However, it should be noted that all 3 methods for grouping MS subjects showed a similar trend. The trend resulted in lower coherence at low frequencies in the more affected MS subjects, compared to controls in the eyes closed condition by both accelerometry and kinematic

methods, although only for the sway range method was this trend significant after Bonferoni correction.

The more affected MS subjects, as defined by sway range, were found to have significantly lower coherence than control subjects at the low frequencies, 0.03Hz and 0.1Hz in the eyes closed condition, with both kinematics and accelerometry, only when grouped by sway range. No other method of severity separation resulted in significant differences between groups, despite the strong resemblance of coherence plots across all three group classifications. These results suggest that neither slowed somatosensory conduction nor reduced motor coordination implicated in walking impairments is the sole contributor to altered balance strategies used by patients with MS.

At the onset of this study, we had hypothesized that a difference in balance strategy, as defined by the coherence and cophase of trunk and shank, would be observed between MS subjects and control subjects, namely an increase in hip strategy at lower frequencies due to slowed somatosensory conduction. If this had been the case, we would expect a significant difference in coherence and cophase among MS subjects depending on the latency of their postural responses.

Similarly, walking speed did not show any significant difference between groups, which suggests that this common clinical measure of severity is not an accurate method of determining postural deficits caused by changes in balance strategies. It is likely that

reduced balance in patients with MS is due to a combination of deficits caused by the disease, which potentially include slow somatosensory conduction and motor coordination, as well as by compensation for these deficits. Unfortunately, sway range is a means of measuring balance abnormalities and is not indicative of any specific physiological deficiency or compensatory mechanism.

Kinematic measures revealed within-group differences in coherence and cophase between adjacent frequencies. These sudden changes in coherence or cophase are indicative of frequencies at which transitions in strategy are occurring. Although not definitive, every group showed a change in coherence at a lower frequency than the change in cophase. These findings suggest the presence of transition frequencies in which coherence between trunk and leg is low, but the two segments are still moving in-phase, inconsistent with both hip and ankle strategy. The simultaneous occurrence of low coherence and low cophase indicates a frequency range which is dominated by the transition from one strategy to the other.

2. Use of Body-Worn Accelerometers to Characterize Balance Strategies

The second aim of this study was to determine how well body-worn accelerometers could be used to determine balance strategies. Coherence plots in all three group classifications, using both accelerometry and kinematics, were distinctly similar in trends, suggesting that use of accelerometers to define balance strategies is promising.

Our results shared common features with the results published by Creath et al., who used kinematics from motion analysis. [65] However, our control subject's coherence had a minimum coherence below 1Hz whereas Creath was near 1Hz. We believe that these differences could be attributed to age or to duration of trials. The Creath et al. study included eight participants, all of which were young, healthy adults (ages 22-37 years). In contrast, the current study involved a large range of ages, from the mid-twenties to mid-sixties, and involved subjects with varying degrees of symptoms and disease progression. Controls were age-matched, which could explain the intra-subject variability in our control group. Elderly subjects experience a decline in stability and have significantly larger sway than young adults, which could lead to altered balance strategies. In addition, trial durations in the Creath study were 364 seconds, whereas our trials were only 30 seconds, which could also result in differences at the lowest frequencies of sway.

All groups of subjects showed stable coherence at very low frequencies, followed by increasing coherence to a peak around 0.43Hz, and then a strong decrease in coherence to a trough near 0.83Hz. The control and mild MS groups often followed these trends, but to varying degrees. The eyes closed condition amplified these distinct features in coherence, which helped draw out significant differences between groups. Both accelerometry and kinematics also showed an increase in coherence after reaching a minimum around 0.83Hz. These features of coherence are also noted by Creath et al., [65] but the frequencies at which they occur differ, which we think could be attributed

to age or trial duration. In order to quantify at which frequency postural strategy changed, we picked two features, the frequency at which cophase crosses 90° and the frequency at which the coherence minimum occurs, both of which appeared to be good indicators of resultant change in balance strategy from ankle to hip. The frequency of the coherence minimum only differed significantly in kinematics between mild and moderate subjects, during the eyes closed condition, when grouped by latency. The value of the cophase at the frequency at which the coherence minimum occurs was also different between the mild and control groups. The significance of these results is not yet clear and will require further investigation to determine the underlying causes.

Mild MS and control subjects changed strategy at higher frequencies, identified by cophase 90° crossing, during quiet stance with eyes closed compared to eyes open, while subjects with moderate MS did not. However, when comparing the value of coherence at these frequencies between eyes open and eyes closed conditions, no significant difference was found. The absence of a difference between value of coherence in eyes open versus eyes closed along with the difference in cophase change suggests that both the mild and control groups are beginning the transition between trunk and leg strategy at different frequencies but that the balance strategy is unaffected because the upper and lower body are not yet coherent. It is not clear why the moderate MS subjects do not change their strategy as much as the other groups, but they may prefer to use hip strategy, even with eyes open, due to the severity of

their impairments or because inflexibility of strategy is easier for a compromised nervous system.

Our study suggests that accelerometry is only partially suitable for determining balance strategies during quiet stance. Prior studies have shown accelerometers to be sensitive to balance parameters such as sway.[83] Our novel results suggest that, although accelerometry is able to distinguish significant differences in coherence, surpassing even kinematic sensitivity, it is unable to determine cophase between the trunk and leg. Previous literature found a change in cophase from 0° to 180° to occur around 1Hz, and kinematic data in this study observed the same results but at a lower frequency of around 0.6Hz. The reason for this difference has yet to be examined but we suggest the coupling of tangential acceleration and gravitational acceleration in the accelerometers as an explanation. The calculations of hip and ankle accelerations involved a correction for accelerometer tilt to account for imperfect sensor placement. However, during balance tasks, movement of the body causes both a tangential acceleration associated with the movement, as well as a gravitational acceleration. Since these two signals were not segregated before analysis, it is possible that the cophase was affected.

Results of coherence analysis show strong similarities between accelerometry and kinematics, including significance between groups and overall coherence trends. Unfortunately, the accelerometers were unable to reliably determine the cophase between the trunk and leg segments. We have suggested a potential explanation for

these results, but further investigation is required to determine whether the limitations of accelerometer measures of postural sway can be mitigated. Therefore, although accelerometers show good potential in determining balance strategies when compared to kinematics, the gold standard, the lack of sensitivity to cophase indicates that a better understanding of what information accelerometers are providing is required before these measures can be useful for characterizing postural movement strategies.

Chapter 5 Summary and Conclusions

Prior to this study, we hypothesized that subjects with multiple sclerosis would present with different balance strategies than control subjects, using kinematics as well as accelerometry. We particularly expected differences in coherence and cophase between mild MS subjects, moderate MS subjects, and controls when grouped by reaction latencies, based on previous research. Contrary to our initial hypothesis, no group differences between mild MS subjects, moderate MS subjects, and control subjects were seen when latency was used to distinguish severity of MS. Similarly, there were no differences between groups when classified by walking speed. Only separation by sway range resulted in the moderate group differing significantly from other groups, suggesting that neither slowed somatosensory conduction nor reduced motor coordination is the sole contributor to altered balance strategies.

We considered two methods of determining change in balance strategy, namely the frequency at which the minimum in coherence occurs and the frequency at which cophase crosses 90°. The minimum in coherence was found to be significantly different between mild and moderate subjects during the eyes open condition, when grouped by latency. A significant difference was noted in the cophase between controls and mild subjects, separated by latency, in the eyes closed condition. Statistical significance was also reached in sway range, eyes open, between moderate and controls, and moderate and mild subjects. The interpretation of these results is not yet clear, and will require further investigation.

Within-subject analysis of frequency found significant differences between frequencies in eyes closed conditions in both latency and walking speed separations with kinematic data. A trend

became apparent which involved a change in coherence at a lower frequency than the change in cophase.

Lastly, accelerometry was used throughout this study, alongside kinematics, the gold standard. Results of coherence analysis showed strong similarities between accelerometry and kinematics, including significance between groups and overall coherence trends. Yet, accelerometry was not able to determine cophase as expected. For this reason, we suggest that accelerometers have the potential to perform on par with kinematics, provided that the cophase detection is resolved.

Appendices

Appendix A

EDSS Score and Clinical Meaning

- **0.0:** Normal Neurological Exam
- **1.0:** No disability, minimal signs on 1 FS
- **1.5:** No disability, minimal signs on 2 of 7 FS
- **2.0:** Minimal disability in 1 of 7 FS
- **2.5:** Minimal disability in 2 FS
- **3.0:** Moderate disability in 1 FS; or mild disability in 3 - 4 FS, though fully ambulatory
- **3.5:** Fully ambulatory but with moderate disability in 1 FS and mild disability in 1 or 2 FS; or moderate disability in 2 FS; or mild disability in 5 FS
- **4.0:** Fully ambulatory without aid, up and about 12hrs a day despite relatively severe disability. Able to walk without aid 500 meters
- **4.5:** Fully ambulatory without aid, up and about much of day, able to work a full day, may otherwise have some limitations of full activity or require minimal assistance. Relatively severe disability. Able to walk without aid 300 meters
- **5.0:** Ambulatory without aid for about 200 meters. Disability impairs full daily activities
- **5.5:** Ambulatory for 100 meters, disability precludes full daily activities
- **6.0:** Intermittent or unilateral constant assistance (cane, crutch or brace) required to walk 100 meters with or without resting
- **6.5:** Constant bilateral support (cane, crutch or braces) required to walk 20 meters without resting
- **7.0:** Unable to walk beyond 5 meters even with aid, essentially restricted to wheelchair, wheels self, transfers alone; active in wheelchair about 12 hours a day
- **7.5:** Unable to take more than a few steps, restricted to wheelchair, may need aid to transfer; wheels self, but may require motorized chair for full day's activities
- **8.0:** Essentially restricted to bed, chair, or wheelchair, but may be out of bed much of day; retains self care functions, generally effective use of arms
- **8.5:** Essentially restricted to bed much of day, some effective use of arms, retains some self care functions
- **9.0:** Helpless bed patient, can communicate and eat
- **9.5:** Unable to communicate effectively or eat/swallow
- **10.0:** Death due to MS

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