

Mechanisms of Sensorimotor Impairment in Multiple Sclerosis

Matthew CheeMing Chua
Marquette University

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MECHANISMS OF SENSORIMOTOR IMPAIRMENT IN MULTIPLE SCLEROSIS

by

Matthew Chua, B.S.

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ABSTRACT
MECHANISMS OF SENSORIMOTOR IMPAIRMENT IN MULTIPLE SCLEROSIS

Matthew Chua, B.S.

Marquette University, 2013

Sensorimotor impairments in people with multiple sclerosis (MS) might alter coordination and balance strategy during functional movements. People with MS often have symptoms such as weakness and discoordination in the lower limbs, resulting in poor walking and balance function. This decrease in function can result in falls, decreased community activity, unemployment, and reduced quality of life. As MS is a progressive disease resulting in a range of dysfunction, the amount of lower limb impairment can cause changes to walking and balance strategies to maintain functional performance. The overall objective of this dissertation was to quantify the impairment at the hip and ankle, and characterize the effects of impairment on walking and balance in MS. To quantify the lower limb impairment, a custom-built robot was used to impose movement to the legs about the hip and ankle joint separately. Joint torque and work done were used as quantitative measures of strength during isometric contraction and coordination during subject assisted leg movements in MS and healthy control subjects. To characterize the effect of impairment on functional movements, motion analysis was used to record kinematic and kinetic parameters during overground walking and during a challenging arm tracking task in standing. Hip and ankle sagittal moments were used to quantify the contribution of each joint to functional movement. The findings from these studies suggest that there is a greater sensorimotor impairment at the ankle than the hip in MS, resulting in a reduced reliance on the ankle during walking and an increased hip versus ankle strategy during upper body movements. This was observed by increased negative work at the ankle during assisted bilateral leg movements, reduced ankle moments during stance in gait, and increased hip versus ankle contribution during arm tracking movements in standing. These results indicate that differential impairment between the hip and ankle can drive changes to walking and balance strategy to maintain functional performance, highlighting the importance of joint specific rehabilitation methods in improving function in MS.

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CHAPTER 1

Introduction and Background

1.1 INTRODUCTION

Sensorimotor impairments in multiple sclerosis (MS) affect the quality of upper and lower body functional movements, resulting in compensatory strategies to maintain functional performance. MS is a progressive disease that affects approximately 300,000 people in the United States and 2 million people worldwide (National Multiple Sclerosis Society, 2012). There is currently no cure for MS, and most prescribed medical or therapeutic treatments serve to slow down the course of MS or manage its symptoms. MS increasingly affects functional systems, causing symptoms such as weakness and discoordination, which can result in difficulties in balance and gait, as well as falls. Due to its progressive nature, people with MS have difficulty adapting to the disease, and immobility and balance problems are still reported to be a major cause of employment loss by people with MS (Glanz et al., 2012; Schiavolin et al., 2012). Although several studies have looked at the changes to movement strategy and lower extremity kinematics in neurologically impaired or aging populations, few studies have been done in the MS population. Hence, further research investigating the relationship between lower limb impairment and walking and balance function in MS is necessary.

The scope of this dissertation was to understand how deficits in function at the hip and ankle affect the contribution of each joint during important daily activities like walking and maintaining balance in MS. This chapter discusses functional impairments, focusing on strength, reflex, and coordination deficits, and how these impairments cause changes to walking and balancing ability in people with MS.

1.2 PATHOPHYSIOLOGY OF MULTIPLE SCLEROSIS

1.2.1 Neuronal Damage in MS

Multiple sclerosis is an inflammatory disease in which the myelin sheaths around the axons of the central nervous system are damaged, leading to demyelination and scarring. MS is generally accepted as being an autoimmune disease, where the person's immune response targets key constituents and producers of myelin like oligodendrocytes, myelin basic protein, and proteolipid protein (Compston and Coles, 2002). The damage to the myelin sheath results in a thinning or complete loss of myelin, or even a transection of the axon with advanced disease progression. During the early phases of the disease, oligodendrocytes are responsible for the rebuilding of the myelin sheath in a process called remyelination. This process does not fully restore the structure and function of the myelin sheath, and it becomes less effective with successive damage to the myelin, resulting in plaques or lesions at the damaged site (Chari, 2007). As the role of the myelin sheath is to increase the speed of neuronal signals that propagate along the myelinated axon, damage to the myelin layer and axon impairs conduction of signals along the nerve. This can cause a broad spectrum of symptoms and functional impairments depending on the location of the lesion.

Lesions can form in various parts of the nervous system including the ventricles of the cerebellum, brain stem, basal ganglia, spinal cord, and optic nerve. MS is considered a disease of the white matter due to the typical appearance of lesions in those areas. However, there has been evidence of lesions appearing in gray matter areas of the

motor cortex (Geurts et al., 2005), cingulate gyrus, cerebellum, thalamus, and spinal cord (Gilmore et al., 2009).

Although demyelination is the main effect of MS, inflammation is also a pathologic hallmark of the disease. In MS, disruptions to the blood-brain barrier make it permeable to lymphocytes, allowing T-cells and B-cells (Iglesias et al., 2001) to enter the central nervous system. These lymphocytes recognize myelin as foreign and attack it, triggering inflammatory processes and stimulating other immune cells like macrophages (Compston and Coles, 2002).

1.2.2 Clinical Characterization of MS

As MS is a progressive disease, the condition of the person with MS could depend on the duration of disease progression, as well as whether there is a period of degenerative autoimmune response known as a relapse or a lull in disease activity known as a remission. The progression of MS has been characterized into four main subtypes – relapsing remitting (RRMS), secondary progressive (SPMS), primary progressive (PPMS) and progressive relapsing (PRMS) — depending on the nature and periodicity of the relapses and remissions (Lublin and Reingold, 1996). Most people are initially diagnosed with RRMS, characterized by unpredictable relapses followed by periods of remission and no new signs of disease activity. This might later progress into SPMS where periods of relapse follow a progressive neurologic decline between acute attacks without any definite periods of remission. People with PPMS experience progressive disability and do not have remission after their initial MS symptoms, while individuals with PRMS have a steady neurologic decline from onset, punctuated by periods of acute attacks.

Because MS is a progressive disease with hugely varying symptoms, clinical characterization of the multiple aspects of impairment is difficult with a single clinical test and scale. Currently, MS is diagnosed using a combination of clinical measures, and radiologic data of the dissemination of MS lesions (McDonald et al., 2001). The degree of MS progression and impairment is typically characterized using the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983), which grades the impairment based on the individual's mobility and dependence on walking assistance, and the Multiple Sclerosis Functional Composite (MSFC) (Cutter et al., 1999; Fischer et al., 1999), which grades the impairment based on upper and lower body function and cognitive function. The Berg Balance Scale (BBS) (Berg et al., 1992) and Timed 25 Foot Walk Test (25FWT) (component of the MSFC), are also used as measures of an individual's balance and walking ability respectively.

1.3 SENSORIMOTOR IMPAIRMENTS DURING BILATERAL MOVEMENT IN MS

1.3.1 Reflex Impairment in MS

MS results in damage to myelin and axons in various parts of the central nervous system, making it likely that motor impairments are rooted in the inability of signals to be efficiently or correctly conducted. Spasticity and co-contraction in MS have been attributed to a lack of short-latency reciprocal inhibition, indicating a deficient control of interneurons, which mediate the inhibitory spinal mechanism between antagonistic muscles (Crone et al., 1994). Abnormal regulation of disynaptic reciprocal inhibition and presynaptic inhibition during dorsiflexion was also identified as being responsible for the abnormal modulation of stretch reflexes in relation to voluntary movement in spastic MS

patients (Morita et al., 2001). Impaired soleus stretch reflexes leading to disruptions in gait have also been demonstrated in MS (Toft et al., 1993; Sinkjaer et al., 1999). However, little has been done to examine the same parameters at the hip in people with. In neurologically impaired populations like stroke and spinal cord injury, hip movement during imposed sinusoidal leg movements is a dominant trigger for spastic reflex activity (Steldt and Schmit, 2004; Wu et al., 2005; Kim et al., 2007; Lewek et al., 2007b), producing multijoint reflexes which involve complex spinal networks (Schmit and Benz, 2002) that are capable of overcoming volitional torque and disrupting motor control (Onushko and Schmit, 2008). In addition to reflex impairments at the ankle, the hip could also play an important role in eliciting abnormal reflex responses during walking in MS.

1.3.2 Impairments in Coordination

Damage to neuronal pathways likely causes dysfunction in coordination, which affects the efficiency of movement in MS. Coordination of the lower limbs is important in performing functional cyclic leg movements, such as walking and pedaling. Interlimb neural mechanisms play an important role in both unilateral (Ting et al., 1998) and bilateral (Ting et al., 2000) tasks. The importance of coordination during a movement is demonstrated during cycling, where intralimb coordination is important for production of large joint torques (Blake et al., 2012), and the power output from the limb is limited by the coordination pattern of the muscles rather than the maximum power output from any one muscle itself (Wakeling, Blake, & Chan, 2010). In neurologically impaired populations, the relationship between active motor tasks and interlimb and intralimb coupling is compromised. For example, stroke survivors demonstrate increased digits and elbow flexion during walking than static positions, as well as an interlimb coupling

related to active motor tasks (Kline et al., 2007). Cruz et al also showed that stroke survivors produce abnormal hip adduction and knee extension torque coupling during isometric hip movements (Cruz and Dhaher, 2008). Impairment of coordination during cyclic hip movement has also been quantified in the stroke population, where abnormalities of paretic hip torque phasing associated with quadriceps overactivity are observed, and are more pronounced during bilateral leg movement and correlated to walking ability in stroke (Hyngstrom, Onushko, Chua, & Schmit, 2010). Coordination impairment in MS has been studied by analyzing grip and load force tracking during static and dynamic manipulation tasks using the arm (Krishnan and Jaric, 2008), as well as during adaptive robot training focused on the upper extremities (Vergaro et al., 2010). Although no studies have analyzed coordination related to functional movement in the lower extremities in MS, it is likely that coordination impairment plays a role in reducing lower limb function resulting in poor gait and balance. It is therefore probable that an imposed cyclic movement of the lower limbs, similar to that used in the aforementioned studies, might reveal the impairments in coordination in the MS population.

Impairment in coordination could result in inefficient work production during movement, and can be characterized by calculating the amount of inappropriate work produced during cyclic movements. Kautz and Brown (1998) quantified the amount of inappropriate work during a movement by measuring negative work, which was defined as the amount of flexion work done during an extension movement, and extension work done during a flexion movement. They characterized the relationship between negative work and impairment in stroke survivors during a pedaling task, showing that the amount of negative work produced is dependent on muscle function (Kautz and Brown, 1998)

and body position (Brown et al., 1997). It is likely that negative work can be used to quantify discoordination in MS during cyclic lower limb movements as well.

1.4 SENSORIMOTOR IMPAIRMENTS DURING WALKING IN MS

1.4.1 Gait Impairments in MS

Gait impairments in MS can likely be traced to inappropriate or inefficient torque production during walking, and attributed to the degree of lower limb impairment. People with MS have a decreased stride length, and decreased ankle, knee, and hip range of motion during gait (Benedetti, Catani, Leardini, Pignotti, & Giannini, 1998; Gehlsen et al., 1986; Holden, Gill, & Magliozzi, 1986; Morris, Cantwell, Vowels, & Dodd, 2002; Rodgers et al., 1999). Abnormal gait has been related to deficits in muscle strength and fatigue, manifested as decreased joint torques (Gutierrez et al., 2005; Thoumie & Mevellec, 2002; White et al., 2004) and joint torque asymmetries even in early stages of MS (Kalron et al., 2011a). The strength of the hamstring and quadriceps have been shown to be reduced in MS compared to healthy controls, and correlated to average walking velocity in MS (Thoumie, 2005). Hence, muscle weakness, reflected as reduced joint torque, appears to be an important contributor to gait impairment in MS.

1.4.2 Hip and Ankle Torque Generation in Gait

In neurologically impaired populations, there is evidence that a redistribution of torques occurs during gait. In neurologically intact individuals, the ankle is usually the primary torque contributor for propulsion (Nadeau, Gravel, Arsenault, & Bourbonnais, 1999). Important parameters like step length and walking speed are limited by plantarflexion peak torque, dorsiflexion range of motion (Mueller, Minor, Schaaf, Strube,

& Sahrman, 1995), and plantarflexor strength (Nadeau et al., 1999). Furthermore, the relative magnitude of torque at each joint during the swing phase remains constant even with different walking speeds (Shemmell et al., 2007). However, in populations with decreased neuromuscular function or neurological deficits, a redistribution of joint torques occurs, giving the hip a more important role in torque generation. This has been shown in elderly adults who demonstrate an increased angular impulse and work at the hip, and decreased angular impulse and work at the ankle compared with young adults during gait (DeVita & Hortobagyi, 2000). This difference between the hip and ankle was present in both active and non-active elderly adults (Savelberg, Verdijk, Willems, & Meijer, 2007), indicating that this redistribution of torques might be related to neuromuscular function rather than muscle weakness. Hip extension torque is the only significant independent predictor for free walking speed, stride length, and cadence in elderly men (Burnfield et al., 2000), indicating the importance of torque generation at the hip in the elderly population. In the stroke population, impaired ankle power generation combined with saturation of hip power generation limits the potential to increase walking speed in lower functioning hemiparetic subjects (Jonkers, Delp, & Patten, 2009). The hip and knee have also been shown to partially offset the reduction in plantarflexor work during stance to swing, demonstrating a redistribution of joint torques to the hip and knee when the ankle is heavily impaired (Chen & Patten, 2008). Although this compensatory mechanism somewhat preserves the ability to walk, the decreased use of the ankle may adversely affect gait in the long run. A study involving stroke survivors with an increased hip effort over ankle effort during maximum cadence implemented a strength improvement program targeting the hip. This resulted in a decrease in gait instead of an

improvement in gait parameters (Milot, Nadeau, Gravel, & Bourbonnais, 2008). By understanding the adapted walking strategies and torque productions during gait in MS, beneficial rehabilitation interventions can be better directed to improve walking function.

As the ability to balance during walking to avoid falling is important for gait performance (Martin et al., 2006; Cameron and Wagner, 2011), a loss of balance function might drive the adaptation of walking strategy and torque redistribution in MS. People with MS favor slower walking speeds, reduce proximity to stability boundaries (Remelius et al., 2008), and reduce ambulatory activity due to poor balance and gait (Cavanaugh et al., 2011). Hence, investigating the relationship between balance impairment and gait performance will provide a better understanding of the underlying mechanisms of gait dysfunction in MS.

1.5 SENSORIMOTOR IMPAIRMENTS DURING BALANCE IN MS

1.5.1 Hip and Ankle Strategy in Maintaining Standing Balance

Maintaining balance during standing relies on the control of various joints, depending on the nature of the perturbation. Two discrete strategies in maintaining balance, namely the ankle and hip strategy, have been proposed (Nasher & McCollum, 1985). These strategies can be used separately or together to produce adaptable control of the center-of-mass (CoM) in the sagittal plane. The ankle strategy repositions the CoM by moving the entire body as a single segmented inverted pendulum through the production of ankle torque. This strategy is used to correct small amounts of postural sway that occur as a result of slow, small perturbations on a firm wide surface. The hip strategy moves the body as a double segment inverted pendulum, with counter phase motions at the ankles

and hip. This strategy is usually used for quick postural adjustments needed to correct larger, more rapid perturbations, or when the support surface is small.

1.5.2 Balance Impairment in MS

People with MS have deficits in balance that affect their functional movement, and likely require an altered balance strategy to maintain balance function. Balance impairment in MS has been widely reported and quantified using clinical measures like the BBS (Karst et al., 2005; Paltamaa et al., 2005; Cattaneo et al., 2006), Dynamic Gait Index (McConvey and Bennett, 2005; Cavanaugh et al., 2011; Gijbels et al., 2012), or stabilometric assessments of COM movement using force plates (Cattaneo and Jonsdottir, 2009). Deficits in balance can result in reduced ability to perform a functional reach (Frzovic et al., 2000), as well as increased postural sway, which has been linked to sensory information processing or motor impairments such as spasticity (Rougier et al., 2007). Abnormal reflex modulation has been implicated in reduced balance ability. For example, the inability to modulate ankle stiffness due to high reflex modulation has been cited as cause of poor postural control (Gatev, Thomas, Kepple, & Hallett, 1999) in healthy controls. Individuals with MS also show a correlation between the level of spasticity, the sway velocity, and the amplitude of the H-reflex from the soleus (Sosnoff, Shin, & Motl, 2010). Different strategies for reflex modulation have been demonstrated between healthy young and older adults in various body positions (Angulo-Kinzler, Mynark, & Koceja, 1998; Koceja, Markus, & Trimble, 1995). Hence, it is likely that impaired reflexes interfere with the ability to maintain balance, requiring an altered balance strategy during continuous voluntary movements in individuals with MS.

1.5.3 Changes to Balance Strategies

The implementation of the hip and ankle balance strategy depends on functional ability, as well as the challenge of the balance task. In healthy individuals, the shift in balance control away from the ankle and towards the hip has been documented during reduced stance widths (Danis et al., 1998; Gatev et al., 1999). In the elderly population, the percentage of ankle strategy and performance in motor tasks decreases with increasing task difficulty compared to a young age group (Liaw, Chen, Pei, Leong, & Lau, 2009). Similarly, Parkinson's disease patients resort to a stiffening strategy to control their balance in postural tasks that imply a mixed ankle and hip strategy (Termoz et al., 2008). Hence, it is likely that people with MS will have a different extent of hip and ankle balance strategy compared to neurologically intact subjects.

Analyses of joint range of motion and joint torque during external perturbations have been used to determine joint strategies for balance during a perturbation. Joint range of motion has been used to indicate a change in the balance recovery strategy from an ankle strategy to a mixed strategy, in response to an increase in platform movement speed which the subjects stood on (Hwang et al., 2009). Analysis of joint torques during an external perturbation has been used to show the addition of hip strategy to ankle strategy in producing a continuum of postural responses (Runge, Shupert, Horak, & Zajac, 1999). Although balance control in response to external stimulations yields important information about the underlying mechanisms of balance, the ability to anticipate postural demands associated with voluntary movements as well as the ability to move the CoM voluntarily and efficiently is relevant in all volitional movements and daily functions. Few studies have been conducted examining balance properties during a dynamic

movement in standing, and none have been conducted in the MS population. Using a self-perturbation to examine the role of the hip and ankle joint will provide information on the usage of an altered hip and ankle strategy in the context of voluntary movements.

1.6 SPECIFIC AIMS

1.6.1 Aim 1: Quantify Hip and Ankle Impairments during Assisted Bilateral Hip and Ankle Oscillations in MS

The purpose of the first study was to quantify the amount of strength and coordination impairment at the hip and ankle during cyclical bilateral “assist” movements, in people with MS. Robotic-assisted cyclic movements were bilaterally imposed first at the hip and then at the ankle of 10 MS subjects, who were instructed to either assist the movements or to remain relaxed during the movements. Joint torque measurements were used to quantify movement patterns and strength during the assisted movements. These measurements were compared to that of 10 neurologically healthy subjects completing the same protocol. We hypothesized that people with MS would have a greater degree of strength and coordination impairment at the ankles than at the hips.

1.6.2 Aim 2: Characterize the Effect of Hip and Ankle Impairments on Overground Walking

In the second study, we investigated the difference in hip and ankle contribution to overground walking in MS. We collected kinematic and kinetic data during overground walking at self-selected speed using a six-camera motion capture system and two force plates. Joint angles and moments from the MS group were compared to 10 neurologically healthy subjects performing the same task. We hypothesized that people with MS would have a larger decrease in ankle moments than hip moments during overground walking, compared to control subjects.

1.6.3 Aim 3: Characterize the Effect of Hip and Ankle Impairments on Balance during a Dynamic, Challenging Balance Task

In the third study, we investigated the difference in hip and ankle contribution to standing, dynamic balance in MS. We used a figure-eight tracking task to challenge balance function, and varied the target speed to alter the difficulty of the task. A six-camera motion capture system and two force plates were used to collect kinematic, kinetic, and muscle activity data to quantify the contribution of the hip and ankle to maintaining balance. The measurements from the MS group were compared to 10 neurologically healthy subjects performing the same task. We hypothesized that people with MS would use the hip more than the ankle during the balance task, compared to control subjects.

CHAPTER 2

Decreased Ankle Function during Bilateral Leg Movement in Multiple Sclerosis

2.1 INTRODUCTION

A better understanding of the deficits in coordination of the ankles and hips in people with multiple sclerosis (MS) could help direct the rehabilitation of functional movements. In people with MS, decreased coordination (Sosnoff et al., 2011), lower extremity weakness (Kent-Braun et al., 1997; Thoumie et al., 2005) and abnormal stretch reflexes (Knutsson and Richards, 1979; Sinkjaer et al., 1993; Toft et al., 1993) often contribute to limitations in functional movements such as gait (Mueller et al., 1995; Nadeau et al., 1999; Milot et al., 2008). While motor impairments likely occur in both the ankle and the hip, there is increasing evidence of a compensatory strategy that includes a redistribution of torques from the ankle to the hip in people with neurological impairments (Nadeau et al., 1999; Lewis and Ferris, 2008; Jonkers et al., 2009). Thus, identifying the relative impairments of the ankles and hips and the subsequent effects on function might shed light on the underlying mechanisms of dysfunction in MS.

Measurement of negative work during bilateral movements is one technique that captures a combination of impairments in the generation of coordinated muscle activity. In neurologically impaired populations, cyclic bilateral leg movements elicit abnormal reflex responses (Steldt and Schmit, 2004; Knikou et al., 2007; Lewek et al., 2007a), resulting in inappropriate muscle activity (Onushko and Schmit, 2008; Onushko et al., 2010) and poor coordination that is correlated to reduced walking function (Hyngstrom et al., 2010). This reduced coordination translates to inefficient work production, manifested as an increase in negative work during bilateral movements (Kautz and Brown, 1998;

Ting et al., 1998). Hence, measurement of negative work during active bilateral leg movements is a viable technique for characterizing the ability to produce concentric muscle contractions that are coordinated with movement – a key feature of the control of muscle activity.

The measurement of negative work during cyclical movements, like other measurements of impairment, would be expected to correlate with sensorimotor function. Deficits such as muscle fatigue, reduced joint torque, asymmetries in joint torque, gait asymmetry, and altered gait parameters can be detected in early stages of MS (Kalron et al., 2011b) and correlate with clinical measures of function, such as the EDSS (Huisinga et al., 2012a). However, the relative impairment of the ankles and hips, and the contribution of impairments at each joint to functional movements involving control of the legs in people with MS are unknown.

In the current study, we measured coordination patterns during active bilateral movements of the hips or ankles in people with MS. Subjects with MS and age-matched controls were asked to assist an imposed, bilateral, sinusoidal oscillation of the hips or ankles. We hypothesized that the MS participants would have an increase in negative work, with larger changes at the ankle than the hip. Further, we postulated that these measures of impairment would correlate to clinical measures of function in MS participants.

2.2 METHODS

2.2.1a Study Participants

Ten subjects with MS (age range: 38-57 yrs, mean age: 50.6 yrs) participated in this study. All MS participants were community ambulators. At the time of the study, three of the ten subjects were taking medication (Ampyra; Acorda Therapeutics, Inc., Ardsley NY) to improve their walking and antispastic medication (Baclofen) to reduce the frequency and intensity of spasms. The clinical features of each subject are described in Table 2-1. Additionally, ten participants (age range: 43-57 yrs, mean age: 51.8 yrs) with no reported neurological damage were recruited into the study as control subjects. Exclusion criteria included: significant cardiovascular problems, respiratory failure, major orthopedic problems including contracture of limbs, joint replacements, significant medical co-morbidity, concurrent illnesses limiting the capacity to conform to study requirements, or the inability to give informed consent. Written informed consent was obtained prior to study participation and all procedures were conducted in accordance with the Helsinki Declaration of 1975 and approved by the Institutional Review Board of Marquette University and the Medical College of Wisconsin.

2.2.1b Clinical Assessment

A variety of clinical tests were used to evaluate each MS subject's function and ability to participate in the study. Manual Muscle Testing (MMT) was used to evaluate the muscle strength of MS subjects to establish general motor function under volitional effort. Scores were given between 0 (no perceivable muscle contractile activity) and 5 (limb position was maintained with full resistance through complete joint range of

motion). Half scores (+, -) were given to graded muscles (Kendall, 1983). The Modified Ashworth Scale (MAS) was used to measure the muscle hypertonia of the MS subjects (Bohannon and Smith, 1987). The subjects' limb segments were moved through a range of motion and the muscle tone in each segment was graded between 0 (no increase in muscle tone during movement) and 4 (large amount of rigidity in flexion or extension during movement) (Table 2-2). The Berg Balance Scale (BBS) was used to evaluate the balance function in MS subjects (Berg et al., 1992). The MS subjects were scored on a 0-4 scale while performing several tasks involving sitting, standing, reaching, and turning, with 0 requiring the most assistance and 4 requiring no assistance while performing the task. The 25 feet walk test (25FWT) was used to evaluate the walking ability of the MS subjects (Kaufman et al., 2000). The MS subjects were required to walk 25 feet repeated in three trials at their own comfortable speed, and the time required was recorded and averaged. The Fatigue Severity Scale (FSS) was a 9-question questionnaire that allowed each subject to rate his level of fatigue between 1 (strong disagreement with the statement) and 7 (strong agreement with the statement), with a typical score of 4 and above indicating that fatigue was a significant factor of the subject's daily activities (Krupp et al., 1989). The Symbol Digit Modalities Test (SDMT) was used to evaluate the cognitive function of the MS subjects (Lewandowski, 1984). The SDMT is a simple substitution task where the subject has to use a reference key to pair specific numbers with given geometric figures within 90 seconds, and the total number of right answers is the score of cognitive abilities. The 9 hole peg test (9HPT) was used to evaluate the coordination function of the MS subjects (Goodkin et al., 1988). The subject was required to place nine pegs into nine holes on a small platform in front of them, and then remove

each peg one by one as quickly and accurately as possible. The test was repeated twice for each hand, and the time required for each iteration was recorded. All clinical tests were completed by a licensed physical therapist prior to beginning the experiment.

Subject specific information is provided in Tables 2-1 - 2-3.

Table 2-1 Clinical Features of MS Subjects

Subject	Age (yrs)	Years with MS	9HPT (s)	SDMT	FSS (of 7)	BBS (of 56)	25FWT (s)	Medications
S01	49	27	22.77	30	6.56	40	11.17	Ampyra, Copaxone
S02	52	15	28.65	40	6.00	46	9.32	Tysabri
S03	56	30	24.98	39	5.11	29	14.71	Baclofen, Ampyra, Interferon Beta, Amantadine
S04	48	8	17.64	50	4.50	55	6.94	Interferon Beta
S05	47	11	24.35	33	5.11	40	12.79	
S06	59	10	18.73	53	4.11	56	7.33	Tysabri
S07	50	5	21.65	48	4.44	47	6.51	Baclofen
S08	38	2	21.30	46	4.67	56	6.52	Baclofen, Ampyra
S09	57	6	27.35	37	4.78	35	18.40	
S10	50	3	20.52	44	4.67	52	7.62	

Table 2-2 Manual Muscle Test Scores of MS Subjects

Subject	Hip Abductors		Hip Flexors		Hip Extensors		Knee Flexors		Knee Extensors		Ankle Dorsiflexors		Ankle Plantarflexors	
	L	R	L	R	L	R	L	R	L	R	L	R	L	R
S01	4	4	4	4	4	4	4	4	5	4	4	4	4	4
S02	4	4	4	4	4	4	2+	5	3+	5	2	5	4	5
S03	4	3	5	5	5	3+	5	5	5	5	5	2+	5	3
S04	4	4	4+	4+	5	5	5	5	5	5	5	5	5	5
S05	4	4	4	4	5	5	4	4	5	5	5	5	5	5
S06	5	5	5	5	5	5	5	5	5	5	5	5	5	5
S07	4	5	4	5	4	5	4	5	4	5	4	5	2	5
S08	4	4	4	4	5	5	5	5	5	5	5	5	5	5
S09	3	4	3	4	5	5	3	4	3	3	4	5	2	5
S10	4	5	4	5	5	5	5	5	5	5	5	5	5	5

Table 2-3 Modified Ashworth Scores of MS Subjects.

Subject	R Knee Extensors	R Knee Flexors	R Ankle PF	R Ankle DF	L Knee Extensors	L Knee Flexors	L Ankle PF	L Ankle DF
S01	0	0	1	0	1	0	0	0
S02	0	0	0	0	0	1	1	0
S03	0	2	2	0	0	2	2	0
S04	0	1	1	0	0	1	1	0
S05	0	1	1	0	1	1	1	0
S06	0	0	0	0	0	0	0	0
S07	0	0	0	0	0	0	0	0
S08	1	1	1	1	0	0	1	1
S09	0	2	2	0	0	2	0	0
S10	0	0	1	0	0	0	0	0

Plantarflexors (PF) and dorsiflexors (DF) abbreviated

2.2.2 *Experimental Setup*

Bilateral hip and ankle isokinetic flexion and extension were imposed on the study participants using a novel leg robot (Figure 2-1). Study participants lay supine with both legs secured in custom, adjustable leg braces. The leg joints were held at 20° knee flexion and 10° ankle plantarflexion during the hip imposed movements, and at 20° hip flexion and 20° knee flexion during the ankle imposed movements. The leg braces were attached to the leg robot that used servomotor drive systems (Kollmorgen, Northampton, MA) to impose oscillations at the aligned leg joints. For hip movements, torque transducers (S. Himmelstein and Company, Hoffman Estates, IL) attached to the leg braces provided measurements of sagittal plane hip, knee, and ankle torques during the imposed movement. Torque transducers (JR3, Woodland, CA) attached to the ankle braces provided measurements of ankle forces and torques during ankle imposed movements. A knee brace was used to restrict medial-lateral movement of the legs during ankle imposed oscillations. Joint position was monitored using optical encoders (US Digital, Vancouver, WA).

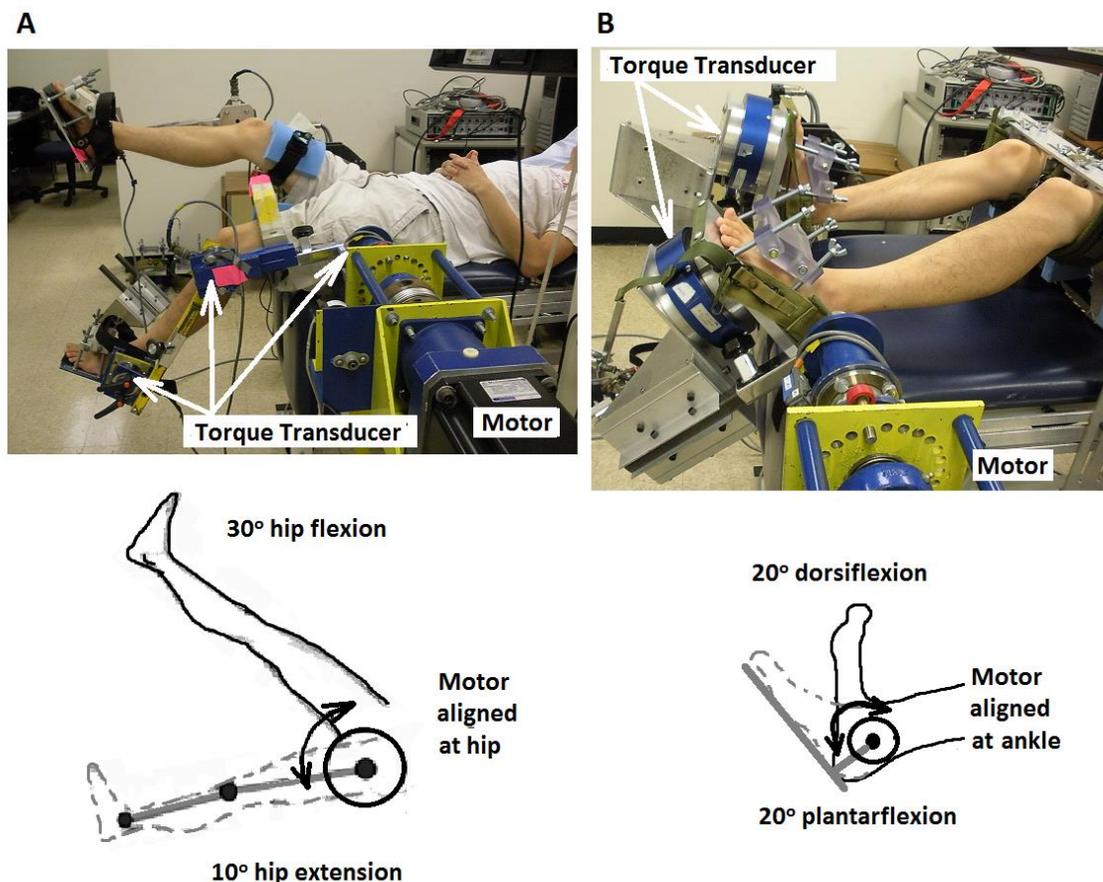


Figure 2-1: Experimental Setup. Leg robot used to impose bilateral hip oscillations and record sagittal plane torques during hip movements (A) and ankle movements (B). Two servomotor systems were used to impose movements about the hip and ankle joints. The hip joint was moved between 30° flexion and 10° extension, while the ankle joint was moved from 20° dorsiflexion to 20° plantarflexion.

Surface electromyograms (EMGs) were recorded bilaterally from the vastus medialis (VM), rectus femoris (RF), vastus lateralis (VL), medial hamstrings (MH), medial head of the gastrocnemius (MG), soleus (Sol), and the tibialis anterior (TA) from all subjects. Recording electrodes (Delsys Inc, Boston, MA) were placed on the cleansed, lightly abraded skin over each muscle belly. EMG signals were bandpass filtered (25-450 Hz) and prior to sampling. Custom LabVIEW software (National Instruments Corp., Austin TX) was used to control joint trajectory and acquire torque and position signals.

All signals were low-pass filtered (500 Hz) prior to data acquisition and sampled at 1000 Hz using a data acquisition card (National Instruments Corp., Austin TX) and a PC.

2.2.3 Experimental Protocol

Hip Oscillation

The subjects lay supine with custom leg braces securing their legs to the leg robot. The hip joints were aligned to the servomotor axes of the leg robot. Oscillations of the legs about the hips were applied using the servomotor apparatus. For calibration of the load cells before the experiment, two hip movements were performed to approximate the biomechanical properties of the leg and leg brace. The torque due to gravity, passive joint resistance, and mass moment of inertia were estimated (further described in section 2.2.4). First, slow, unilateral incremental movements (5° steps) were imposed about the left and right hip to estimate the torque contribution due to gravity and passive joint resistance throughout the range of motion. Second, fast 1.5 Hz leg oscillations were imposed to each leg, moving through a 30° range of motion (25° hip flexion to 5° hip extension) to determine the combined inertial constant of the leg and leg brace. Subjects were instructed to remain as relaxed as possible during these movements.

For the hip oscillation protocol, the subject's legs were moved at 180° out of phase through a 40° range of motion (30° hip flexion to 10° hip extension) for twenty cycles. The knee and ankles were held isometrically in the leg braces at (20° knee flexion, 10° ankle plantarflexion). The leg movements were performed at 0.75 Hz, and study participants were instructed to either assist the imposed motions (active movement), or to remain inactive during the imposed motions (passive movement). Subjects were not

provided with any feedback on their performance during the trials. The trials started with two passive trials, followed by two active trials, and then another two active trials.

Maximal voluntary contraction (MVC) measures were performed before and after the hip oscillation trials. Flexion and extension MVCs on each hip were tested separately, with rest time in between each test.

Ankle Oscillation

After the hip oscillation protocol had concluded, the subject was unsecured from the hip setup of the leg robot and allowed to take up to a 10 minute break. When ready, the subject again lay supine in the leg robot, with custom ankle braces securing the feet and ankles to the leg robot. The ankle joints were aligned to the servomotor axes of the leg robot and bilateral oscillations about the ankles were applied using the servomotor apparatus. Similar to the hip oscillation protocol, two ankle movements were performed to approximate the biomechanical properties of the feet and ankle brace prior to the ankle protocol. The torque due to gravity, passive joint resistance, and mass moment of inertia were estimated in a manner similar to the hip testing. Slow, unilateral incremental movements (5° steps) were imposed about the ankle to estimate the torque contribution due to gravity and passive joint resistance. Fast 1.5 Hz leg oscillation movements were imposed to each foot, moving through a 20° range of motion (15° ankle dorsiflexion to 5° ankle plantarflexion) to determine the combined inertia of the feet and ankle braces. Subjects were instructed to remain as relaxed as possible during these movements

For the ankle oscillation protocol, the subject's feet were moved 180° out of phase through a 40° range of motion (20° ankle dorsiflexion to 20° ankle plantarflexion) for twenty cycles. The hip and knee were held isometric in the knee braces (20° hip flexion,

20° knee flexion). Movement of the ankles was performed using the same protocol used for the hips.

2.2.4 Data Analysis

The biomechanical properties of the leg and leg brace were measured to calculate the torque due to active muscle contraction. The measured torque had to be corrected for gravitational torque, torque due to passive joint resistance, and inertial torque. The general equation used to calculate the active torque τ_{joint} for each joint was:

$$\tau_{\text{joint}} = \tau_{\text{measured}} - \tau_{\text{passive/gravity}} - \tau_{\text{inertia}}$$

where τ_{measured} was the raw, measured torque for a specific joint, $\tau_{\text{passive/gravity}}$ was an approximated torque produced by the passive joint resistance and gravity, and τ_{inertia} was the calculated torque based on the inertial properties of the leg and leg brace.

The technique used to calculate the torque due to active muscle contraction is the same as previous studies (Steldt and Schmit 2004, Onushko and Schmit 2007). Briefly, the $\tau_{\text{passive/gravity}}$ was estimated by fitting a polynomial curve (torque vs hip angle) to the trials in which the leg was moved in slow incremental steps through the range of motion. Torque data from the hold periods were used to estimate the combined gravitational and passive joint resistance. The polynomial function was then used to estimate the $\tau_{\text{passive/gravity}}$ during the movement trials and subtracted from the measured torque. Similarly, the inertial coefficient was estimated from the trials with rapid oscillations in midrange. The $\tau_{\text{passive/gravity}}$ was first subtracted from the measured torque. The hip angular acceleration was calculated from the movement trajectory and the inertial coefficient was then identified using a regression. This inertial coefficient was then

applied to the test trial acceleration data to calculate $\tau_{inertia}$, which was subtracted from the measured torque.

After subtraction of $\tau_{passive/gravity}$ and $\tau_{inertia}$, the remaining torque signal was the active joint torque produced by the subject. All torque signals were then low-pass filtered (5Hz) using a second order zero phase delay Butterworth filter.

Phase Analysis

A phase analysis was performed on the active torques to determine the timing of activity with respect to the hip and ankle position during the imposed movements. The timing of responses was quantified using circular statistics (Batschelet 1981) as described previously (Onushko and Schmit 2007). Briefly, torque signals were separated into flexion and extension components, and the cycle period was normalized to a 360° polar plot, with 0° being full flexion and 180° defined as full extension. The peak torques for each oscillation cycle were calculated and averaged, allowing each data point on the polar plot to represent each subject's peak torque and corresponding phasing during oscillation.

To analyze the phasing of the torques independent from their magnitude, the peak torques from each cycle were normalized to a unit vector, and averaged across trials. The resulting mean vector was defined by its magnitude (0-1 range) and phase angle. If the phasing of the vectors was identical for all cycles, the magnitude would be 1; whereas if the phasing was random, the mean vector amplitude would be close to 0. To examine the phasing across subjects, the mean vector for each subject was again normalized to a unit vector and a mean vector across subjects within a group was calculated. The Rayleigh Test was first used to determine if the torques generated had significantly similar phasing within groups ($p < 0.05$). The significance of the mean angle from the peak torques

generated across subject groups (MS vs. Controls) was statistically tested using the Watson-Williams Test ($p < 0.05$).

Torque Amplitude Analysis

The peak flexion and extension torques for the hip and ankle were determined in order to identify differences in volitional effort between the subject groups. The left and right leg joint torque signals were separated into flexion and extension components, and the peak torque was identified for each cycle of movement. These values were then averaged between both legs of each subject, averaged within each subject, and across groups for analysis.

MVC Analysis

The flexion and extension MVCs at the hip and ankle of each leg were first determined separately to estimate the subject's volitional strength and for comparison between groups. Second, the flexion and extension MVCs were separately averaged across each joint (e.g. averaged right and left hip flexion) to obtain a measure of the subject's flexion strength and extension strength at the hip and ankle. Third, the flexion and extension MVCs were averaged together at the hip and at the ankle to obtain an overall measure of volitional strength at each joint. All MVCs were normalized by the subject's body weight.

Negative Work Ratio Analysis

The amount of positive and negative hip and ankle work done during active leg oscillations was calculated to determine the efficiency of active movement at the hip and ankle. The joint torque signals were separated into flexion and extension components,

and the area under the temporal torque signal was calculated as work. The amount of work was then further identified as being either positive or negative work, where positive work would correspond to joint torque in the same direction as the movement of the leg robot (e.g. flexion torque during the flexion phase of movement), negative work was associated with torque countering the movement of the leg robot (e.g. extension torque during the flexion phase of movement), and total work being the sum of the positive and negative work magnitudes.

The analysis of negative work ratio parameters was similar to that of the MVC analysis. The flexion and extension negative work ratios at the hip and ankle of each leg were first determined separately to estimate the subject's coordination efficiency and for comparison between groups. Then the flexion and extension negative work ratios were separately averaged across each joint (e.g. averaged right and left hip flexion) to obtain a measure of the subject's flexion negative work ratio and extension negative work ratio at the hip and ankle. Lastly, the flexion and extension negative work ratios were averaged together at the hip and at the ankle to obtain an overall measure of coordination efficiency at each joint.

2.2.5 Statistical Analysis

For the analysis of phasing of torques, the Rayleigh Test was used to determine if the torques had significantly similar phasing within groups ($p < 0.05$). The significance of the mean angle from the peak torques generated across subject groups was statistically tested using the Watson-Williams Test ($p < 0.05$).

A one-way ANOVA (SPSS Inc., Chicago IL) was used to compare the between group differences in MVCs, peak torque during active bilateral leg movement, and

negative work ratios at the hip and at the ankle. A two-way ANOVA was also used to compare differences in negative work ratio between the MS and control group with the negative work ratios as the dependent variable, and subject group (MS or control) and leg joint (hip or ankle) being the fixed factors. Significance was accepted at $p < 0.05$. Outliers were identified as having data values more than two standard deviations from the mean, and excluded from the group averaged data.

A linear regression was used for statistical analysis of the relation between the joint parameters and clinical scores of BBS and 25FWT. Cook's distance analysis was used to identify outliers to the regression, and separate regressions were calculated excluding the outliers.

2.3 RESULTS

2.3.1 *Peak Torque Phasing and Amplitude*

In this study, we tested whether strength and coordination during active bilateral leg movements were significantly different between MS and control subjects. In MS subjects, we also tested correlations between measurements and impairment in people with MS. Specifically, we analyzed flexion and extension MVCs, as well as peak torques and negative work produced during active bilateral leg movement at the hip and ankle.

Peak flexion and extension torque amplitudes and phasing during assisted movement were used to compare the overall coordination patterns between the MS and control groups (Figure 2-2) and showed that patterns of peak torque production were similar between the MS and control group. Normalized torques and their corresponding polar angles were calculated from peak torque values and angles for analysis of peak torque phasing (Table 2-4) to determine if the torques were similarly phased within groups using Rayleigh's Test, and if the phasing of torques between groups was similar using Watson-Williams Test (Table 2-5). Peak torque phasing was not significantly different between the MS and control group ($p>0.05$), indicating similar phasing performance between both groups during the active bilateral movement

Peak hip and ankle torque and phasing parameters were averaged between both legs for each subject and within groups to get an estimation of the overall torque and phasing within the MS and control groups. For the control group, peak hip flexion and extension torque occurred at a polar angle of approximately 50° , corresponding to an anatomical angle of 18° hip flexion. For the MS group, peak hip flexion and extension

torque occurred at a polar angle of approximately 35° , corresponding to an anatomical angle of 22° hip flexion. At the ankles, the control group's peak ankle extension and flexion torque occurred at a polar angle of approximately 84° , corresponding to an anatomical angle of 1° ankle flexion which is close to the neutral position, while the MS group's peak ankle extension and flexion torque occurred at a polar angle of approximately 65° , corresponding to an anatomical angle of 5° ankle flexion (Table 2-6). Overall, peak torque production occurred slightly earlier in the MS group compared to the control group, but the differences were not significant ($p>0.05$).

Peak torque amplitudes during active bilateral leg movement were slightly higher at both the hip and ankle in the control group compared to the MS group, but the differences were not significant between groups (Table 2-7), indicating a similar self-selected sub-maximal effort level for the MS and control group.

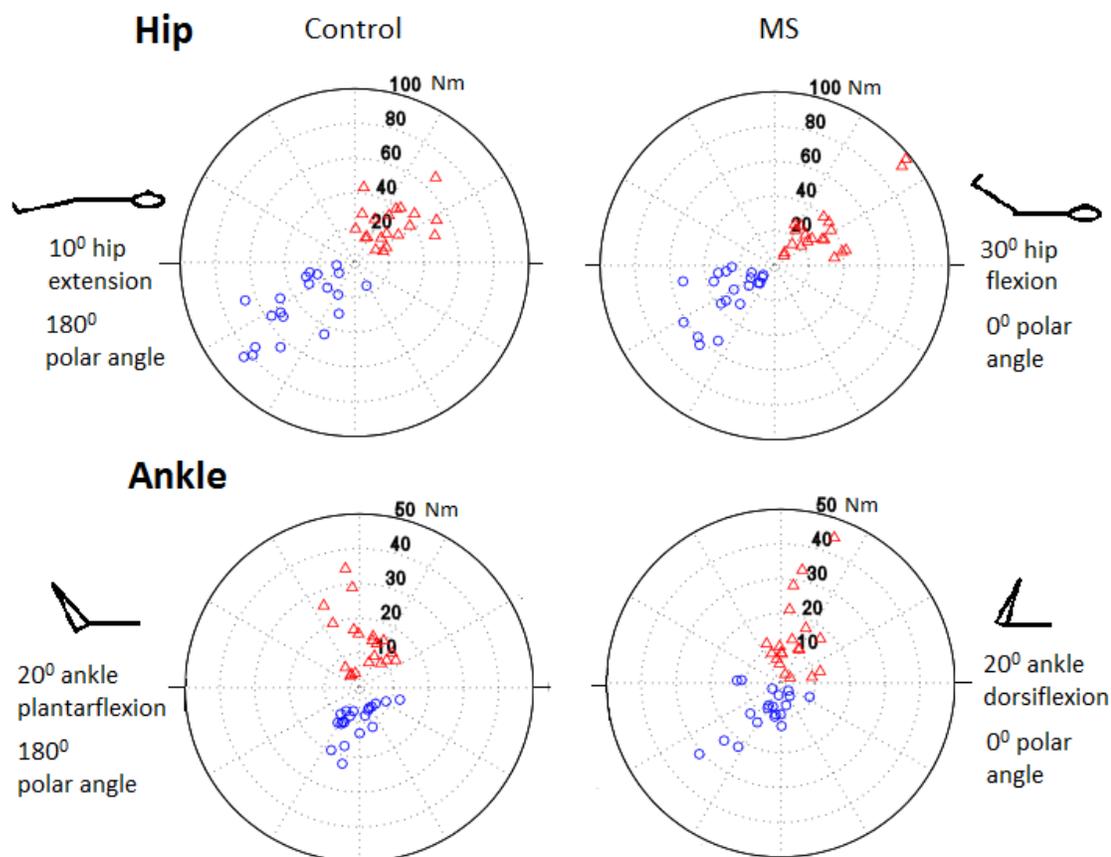


Figure 2-2: Group Averaged Polar Plots of Peak Torque. Subjects' average right hip and ankle peak flexion (O) and extension torques (Δ) for two active assist trials per subject. Full joint flexion corresponds to 0° and full extension corresponds to 180° . The direction of movement is counterclockwise on the polar plot. Torque magnitudes (Nm) are represented radially on the polar plots. No significant differences were found between MS and control subjects during right and left leg assisted movements for peak torque phase and amplitude data ($p > 0.05$).

Table 2-4: Normalized Group Torques and Polar Angles

			Control		MS	
			τ	Θ	τ	Θ
Hip	Right	Flexion	0.850	38.715	0.933	28.369
		Extension	0.901	48.518	0.918	37.381
	Left	Flexion	0.799	61.923	0.795	42.147
		Extension	0.842	57.523	0.837	39.644
Ankle	Right	Flexion	0.761	87.686	0.733	64.495
		Extension	0.820	83.721	0.810	72.710
	Left	Flexion	0.823	81.624	0.565	65.635
		Extension	0.901	80.651	0.736	60.164

Peak torques from each cycle were normalized to a unit vector, and averaged across the corresponding trials. The resulting mean vector τ was defined by its magnitude (0-1 range) and phase angle Θ ($^{\circ}$). If the phasing of the vectors was identical for all cycles, the magnitude would be 1, whereas if the phasing was random, the mean vector amplitude would be close to 0.

Table 2-5: Rayleigh Test and Watson-Williams Significance

			Rayleigh p values		Watson-Williams p value
			Control	MS	
Hip	Right	Flexion	.000171	.000017	.425
		Extension	.0000361	.0000203	.346
	Left	Flexion	.000627	.000691	.278
		Extension	.000214	.000247	.265
Ankle	Right	Flexion	.00150	.00260	.263
		Extension	.000377	.000481	.521
	Left	Flexion	.000349	.0368	.505
		Extension	.0000369	.00240	.238

All parameters were significant for the Rayleigh Test ($p < 0.05$), indicating that there was a directedness in the phasing of torques in each group. All parameters were not significant for the Watson-Williams Test ($p > 0.05$), indicating that the phasing of torques between groups was similar.

Table 2-6: Group Polar Angles and Equivalent Anatomical Angles of Peak Torque

		Polar angle (°)		Anatomical angle (°)	
		Control	MS	Control	MS
Hip	Flexion	50.319	35.258	18.818	22.165
	Extension	53.020	38.512	18.218	21.442
Ankle	Flexion	84.655	65.065	1.188	5.541
	Extension	82.186	66.437	1.736	5.236

Values are averaged from the left and right legs. Polar angles are referenced from the beginning of the cycle; e.g. flexion polar angles are referenced from cycles starting from full extension ending at full flexion. Anatomical angles are referenced from the anatomical 0° position of the joint.

Table 2-7 Group Peak Torques

			Control		MS		p value
			τ	s.d.	τ	s.d.	
Hip	Right	Flexion	41.602	22.006	32.360	17.918	.317
		Extension	31.687	13.806	35.381	22.820	.667
	Left	Flexion	30.212	12.372	25.923	10.920	.422
		Extension	42.072	21.842	39.279	21.019	.774
Ankle	Right	Flexion	11.238	3.935	10.605	7.017	.806
		Extension	14.350	7.844	13.688	11.002	.878
	Left	Flexion	10.162	2.955	9.649	4.989	.783
		Extension	17.667	7.694	15.305	10.563	.575

Torques (τ) and standard deviations (s.d.) are in Nm. All parameters were not significant (One way ANOVA $p>0.05$), indicating that the peak flexion and extension torques between groups was similar.

2.3.2 Strength and Coordination Impairments

MVCs were measured to estimate of the subject's strength and impairment at the hip and ankle. Separate flexion and extension MVCs as well as total MVCs for the hip and ankle were calculated and found to be not significantly different between groups ($p>0.05$) (Table 2-8).

Table 2-8: MVC Group Significance and Regression Parameters

		Between	Regression			
		group	BBS		25FWT	
		significance	R ²	p	R ²	p
		p				
Hip	Ext	.453	.265	.127	.134	.299
	Flex	.742	.350	.072	.383	.056
Ankle	Ext	.218	.086	.410	.024	.668
	Flex	.117	.195	.202	.080	.429
Hip	Total	.753	.456	.032	.377	.059
Ankle	Total	.150	.139	.288	.046	.553

Separate flexion and extension MVCs as well as total MVCs were not significantly different between groups (ANOVA $p > 0.05$). Regressions between MVCs and clinical measures were generally weak, with the hip total MVC showing the best regression to the BBS and 25FWT (highlighted in bold).

Negative work ratios at the hip and ankle were calculated to describe the efficiency of coordination during bilateral leg movement. Single subject ensemble torque traces of a typical MS and control subject demonstrate that the negative work produced during extension and flexion phases of movement in the MS subject are larger than the control (Figure 2-3). During the calculation of separate hip and ankle negative work ratios, one outlier (S01) was identified as having ankle flexion negative work ratio greater than two standard deviations from the group mean, and was omitted from the calculation of the ankle flexion negative work ratio group mean. Hip and ankle flexion negative work ratios (ANOVA, hip $p = 0.042$, ankle $p = 0.037$), as well as ankle total negative work ratio (ANOVA, $p = 0.040$) were found to be significantly different between groups (Figure 2-4). Two-way ANOVA analysis between groups with negative work ratio as the dependent variable and subject group and joint (hip and ankle) as the fixed factors showed that there was a significant difference in negative work ratio between the MS and control group (Two-way ANOVA $p = 0.031$).

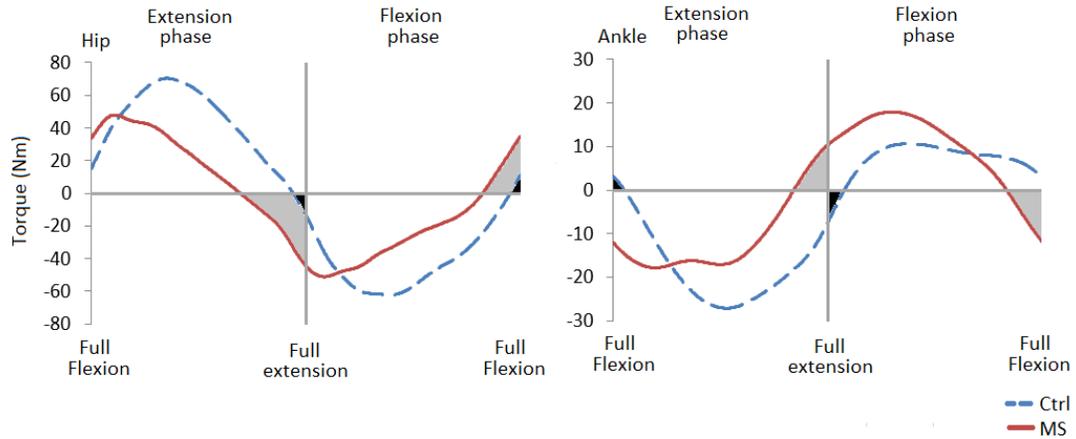


Figure 2-3: Single Trial Ensemble Average Torque. Single subject (MS: S03 and control: C01) torque traces showing negative work (shaded area under the curve) produced during active bilateral movement at the hip and ankle. For hip movement, extension torque is positive and flexion torque is negative. For ankle movement, plantarflexion torque is negative and dorsiflexion torque is positive. The MS subject was observed to produce more negative work than the control subject.

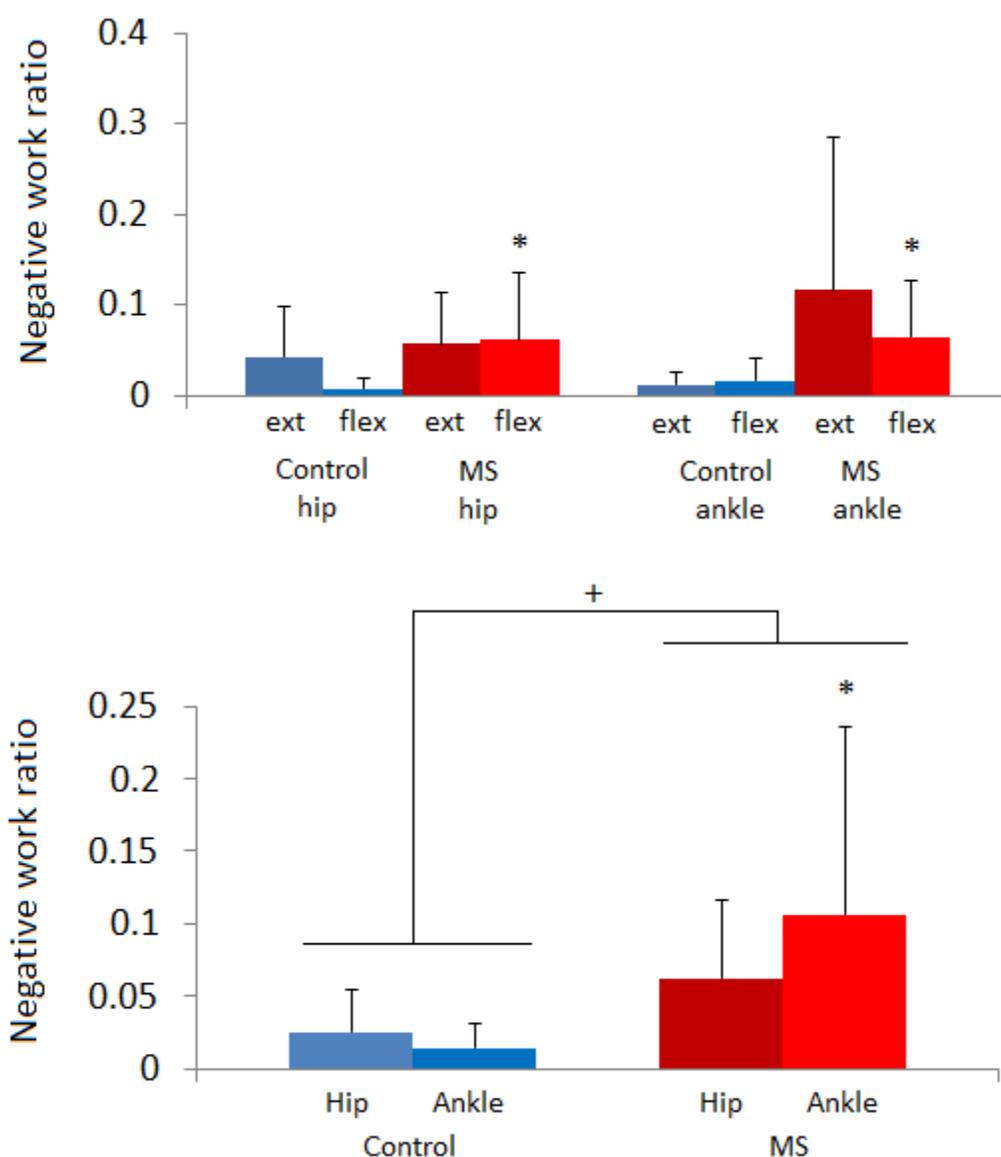


Figure 2-4: Group Hip and Ankle Negative Work Ratio. Top graph: The MS group had a significantly larger negative work ratio during hip and ankle flexion than the control group (hip flexion ANOVA $p=0.042$, ankle flexion ANOVA $p=0.037$). Bottom graph: The total (average of flexion and extension) negative work ratio at the ankle was significantly different between groups (ANOVA, $p=0.040$), and close to significance at the hip (One-way ANOVA, $p=0.079$). Overall negative work was also significantly different between the MS and control group (Two-way ANOVA $p=0.031$). One way ANOVA significance is indicated with *. Two way ANOVA significance is indicated with +. Significance was accepted at $p<0.05$. Standard deviation bars are indicated.

Regression analyses of MVC and negative work ratio to clinical measures of BBS and 25FWT were used to determine the relationship between strength and coordination

dysfunction and clinical measures of impairment. Regression analyses of MVC to BBS and 25FWT showed no significant trends (Table 2-8), with the hip total MVC showing the best regression (BBS $R^2 = .456$, $p = .032$; 25FWT $R^2 = .377$, $p = .059$).

Regression analyses of separate flexion and extension negative work ratio (Figure 2-5) as well as total negative work ratio (Figure 2-6) at the hip and ankle to clinical measures of BBS and 25FWT showed consistent trends of increasing negative work ratio with increasing clinical measures of impairment. Regression outliers were identified using Cook's distance analysis, and regression parameters were calculated with and without the outliers. The regressions between negative work ratio and clinical measures were consistently stronger at the hip than the ankle, with hip flexion and extension, as well as hip total negative work ratio showing much higher R^2 and lower p values than at the ankle (Table 2-9).

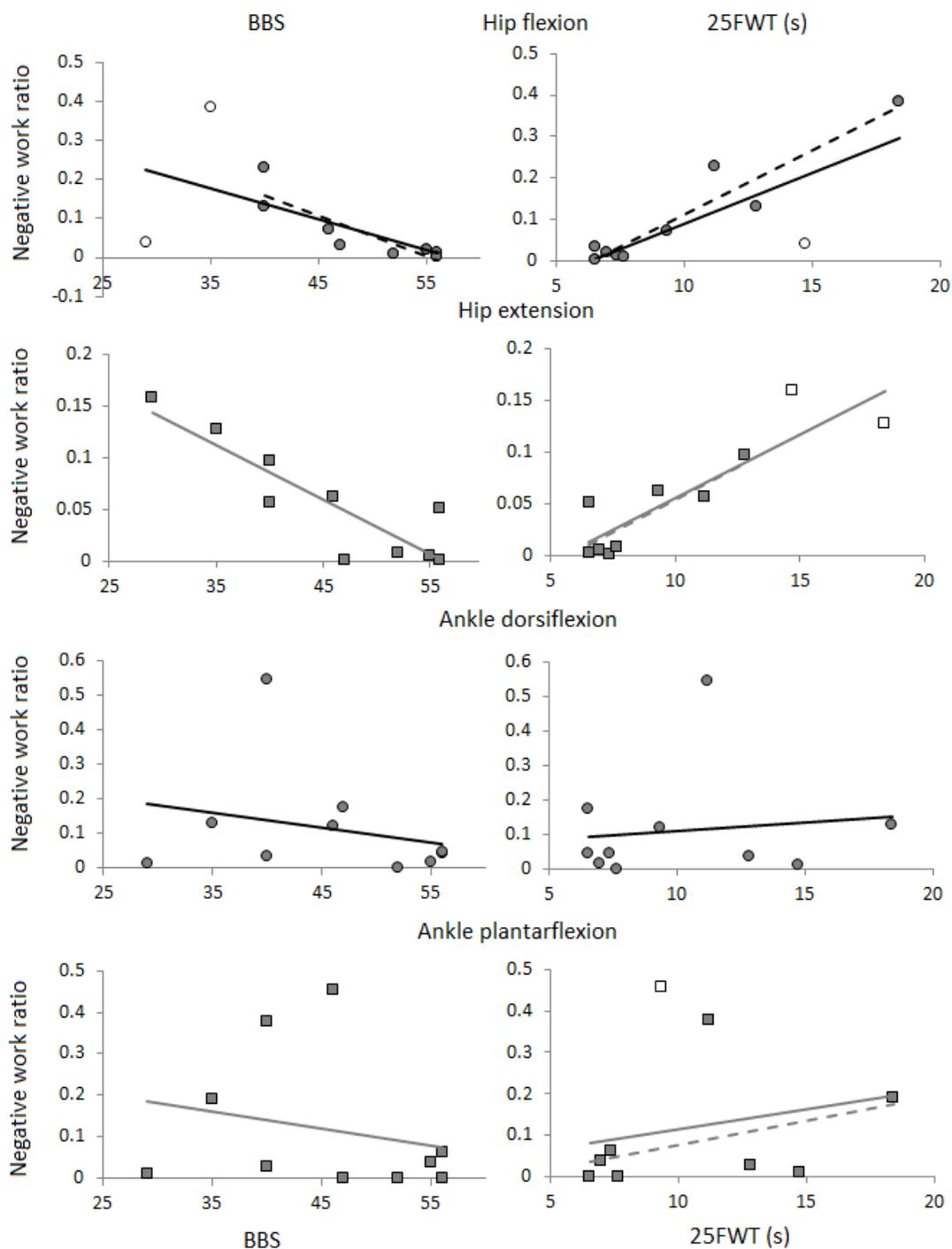


Figure 2-5: Negative Work and Clinical Measures Regressions. Flexion and extension negative work ratios at the hip and ankle were plotted against the BBS and 25FWT. Regression outliers (open markers) were identified using Cook's distance analysis and separate regression lines were plotted with and without the outliers. The MS negative work ratios generally increased with increasing impairment, with the hip negative work ratios being stronger predictors of clinical measures than the ankle negative work ratios.

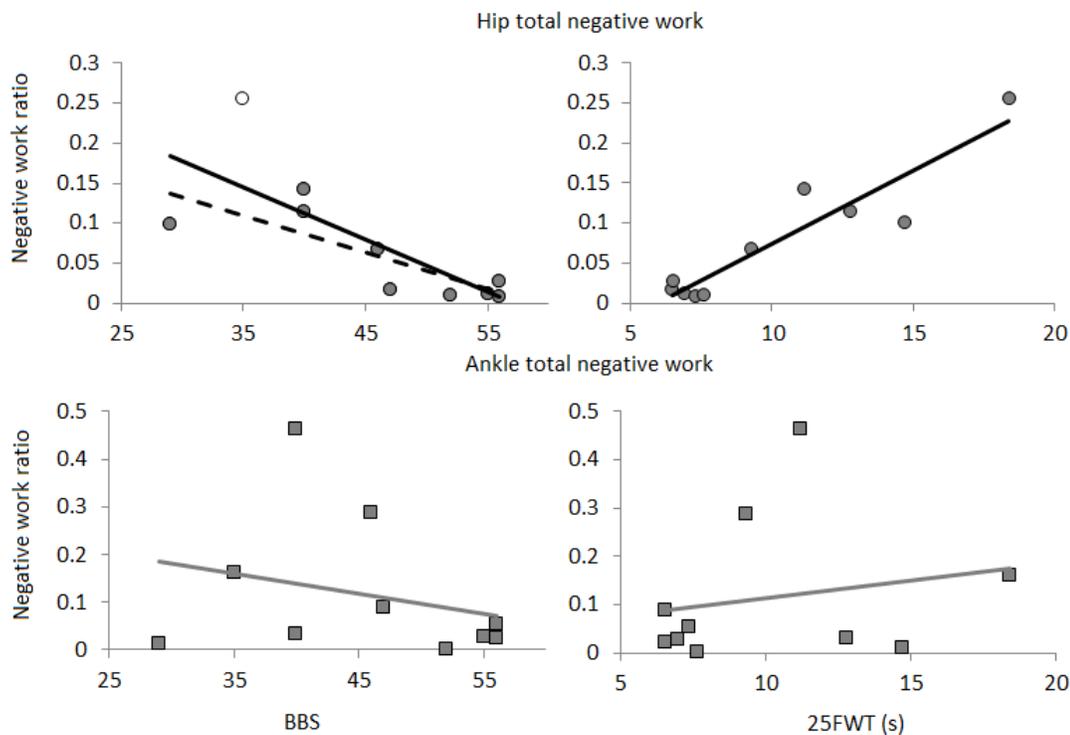


Figure 2-6: Negative Work and Clinical Measures Regressions. Total negative work ratios at the hip and ankle were plotted against the BBS and 25FWT. Regression outliers (open markers) were identified using Cook's distance analysis and separate regression lines were plotted with (solid lines) and without the outliers (dashed line). The MS negative work ratios generally increased with increasing impairment, with the hip negative work ratios being stronger predictors of clinical measures than the ankle negative work ratios.

Table 2-9 Negative Work Ratio Regression Parameters

	BBS		25FWT	
	R ²	p	R ²	p
Hip flexion	.355	.069	.643	.005
	<i>.762</i>	<i>.005</i>	<i>.901</i>	<i>.000</i>
Hip extension	.774	.001	.787	.001
			.679	.012
Ankle flexion	.063	.483	.015	.738
Ankle extension	.052	.526	.053	.521
			.156	.293
Hip total	.589	.010	.863	.000
	<i>.653</i>	<i>.008*</i>		
Ankle total	.070	.460	.0380	.588

Negative work ratio and clinical measure regression parameters were first calculated including all points, then recalculated to exclude regression outliers based on Cook's distance analysis (rows are italicized). Hip flexion, extension, and total negative work ratio showed the strongest regression to the BBS and 25FWT (highlighted in bold).

2.4 DISCUSSION

Results from this study showed that there is a reduced ability to coordinate bilateral movement at the hips and ankles in people with MS. Despite producing similar peak torque amplitudes and phasing during active movement, people with MS had a higher negative work ratio than the control group, particularly during hip and ankle flexion. This effect was more pronounced at the ankle when both flexion and extension negative work ratios were averaged. Furthermore, the negative work ratio at the hip was strongly correlated to clinical measures of balance and gait.

2.4.1 Deficits in Reflexes and Work Production

During bilateral joint movements, overall patterns of active torque were similar between the MS and control group, denoted by peak torque amplitudes and phasing that were not significantly different between groups. Although each subject was instructed to exert a strong but sub maximal level of effort when assisting the movement, the self-selected effort in both groups resulted in similar peak torque amplitudes and phasing. This indicates that the MS subjects were able to utilize a strategy that allowed them to perform the task despite physical impairments. This similarity in general performance between both groups might be attributed to two main factors - comparable group MVC strength and the simplicity of the movement task. Although the subject movement ability ranged from low (BBS=29, 25FWT=18.4s) to high function (BBS=56, 25FWT=7.30s), most MS subjects had 'good' strength measured via the manual muscle test (total average Manual Muscle Test score=4.5), and the group MVCs as a whole were not significantly different between both groups. Thus, the ability of MS subjects to generate joint torque

was not significantly compromised compared to the healthy control subjects.

Furthermore, the bilateral leg movement task was a simple, controlled, single degree of freedom motion, where the effect of gravity and balance was eliminated, likely allowing the MS subjects to perform similarly to the healthy controls.

Although MS subjects were able to produce similar peak torque amplitudes and phasing during bilateral movement, the pattern of work produced during the movement was different from the control subjects. Generally, the MS subjects had a higher negative work ratio than the control subjects, particularly during the flexion phase. Furthermore, when considering the total negative work ratio (consisting of the average of flexion and extension negative work ratio per joint), the negative work ratio at the ankle was significantly higher in the MS group. As the phasing of peak torque was similar between groups, this negative work reflected errors in the early and late parts of the movement cycle, particularly around the transitions between flexion and extension.

Spasticity may have played a role in the increased negative work ratio in MS subjects. Although the MS subjects did not have high levels of spasticity during the clinical examination (total average spasticity from Modified Ashworth Score=0.425) or during passive bilateral movement at the hip and ankle, we cannot eliminate the possibility of spastic reflexes influencing active, out-of-phase, bilateral movement. Imposed sinusoidal leg movements reveal abnormalities in reflex modulation in human spinal cord injury (Steldt and Schmit, 2004) and other neurologically impaired populations (Knikou et al., 2007; Lewek et al., 2007a). The effect of abnormal reflex modulation is exaggerated during flexion (Knikou et al., 2006), end of range of movement (Schmit et al., 2000), and extended muscle lengths (Schmit et al., 2002;

Knikou et al., 2006). This is consistent with MS subjects in this study having a larger negative work ratio during flexion, with negative work being produced near flexion-extension transitions and at the ends of range of motion. At the ankle, greater torque asymmetries (Kalron et al., 2011a) and impaired modulation of the stretch reflex along with increased ankle joint stiffness (Sinkjaer et al., 1996a) might contribute to an increase in negative work during ankle flexion. The effects during ankle extension are likely to be muted due to an absence of reflex-mediated responses in the ankle flexors in MS (Toft et al., 1993). It is probable that the bilateral nature of the movement enhanced spastic reflex excitability (Onushko and Schmit, 2007) in the MS subjects, which resulted in co-contraction of antagonistic muscles during movement, similar to stroke subjects (Hidler et al., 2007). In subjects with a high spasticity, the reflex responses might trump volitional effort and disrupt motor control (Onushko and Schmit, 2008; Onushko et al., 2010).

2.4.2 Deficits in Coordination and Functional Movement

In the current study, the MS subjects' reduced ability to coordinate muscle activity at the transition points of bilateral movement points towards a neurological deficit in simultaneously controlling the timing of activity in multiple muscles. These deficits could be related to timing of flexors and extensors at a single joint, or in the coordination of interlimb muscles. Note that interlimb control mechanisms are important for unilateral pedaling tasks (Ting et al., 1998) as well as for coordinating activity between muscles that perform antagonistic functions on opposite sides of the body (Ting et al., 2000). Similarly, the coordination of muscle timing across joints and across limbs is important for the generation of power during pedaling (Wakeling et al., 2010) and the

coordination of activity in multiple muscles crossing the same joint is important for pedaling efficiency (Blake et al., 2012). In people with neurological injury, these coordination patterns can become disrupted. Interlimb coupling between the arm and leg is altered after stroke (Kline et al., 2007), and intralimb coordination is substantially compromised during pedaling. In the current study, the compromise to timing of muscle activity in MS subjects during transition points whilst maintaining peak torque output and timing is consistent with a preferential loss in coordination in people with MS.

Features of the bilateral motor task used in the current study might be altered to increase sensitivity to motor deficits in people with MS. The deficits in coordination in people with MS appeared to be direction-specific, as a larger negative work ratio during joint flexion was observed. The role of muscles as an extensor or flexor depends on movement rate (Neptune et al., 1997) and the effective work production in muscles is differently affected in stroke survivors, depending on function (Kautz and Brown, 1998). Thus, altering the movement trajectory to examine differences in flexor and extensor coordination might be warranted. In the current study, the bilateral leg movement was done at a fairly low frequency which was likely within the comfortable speed of movement for MS subjects, allowing them to produce torques comparable to the control subjects. As effective work production diminishes at higher rates in healthy controls (Neptune and Herzog, 1999) and elderly (Clark et al., 2010), further studies using the same experimental paradigm with higher movement rates might exacerbate the neurological deficits and highlight effects of movement frequency on coordination in people with MS.

2.4.3 Relationship between Inefficient Work Production and Impairment

Although the MS group showed a higher negative work ratio at both the hip and ankle compared to the control group, a strong relationship between negative work ratio and clinical measures of walking and balance was manifested only at the hip. This observation indicates that the hip plays the more important role in determining functional ability and would suggest that the ankle has become dissociated from functional importance. An increased dependence on the hip might be related to the greater impairment at the ankle, reflected by the larger negative work ratio at the ankle, compared to the hip in MS subjects. This would suggest that people with MS change their motor control strategy to increase the contributions from the hip, compared to the ankle. This notion is consistent with evidence that impaired hip coordination is correlated with poor walking function in stroke (Hyingstrom et al., 2010), and an increased reliance on the hip in MS (Thoumie, 2002), stroke survivors (Jonkers et al., 2009), and the elderly (DeVita and Hortobagyi, 2000; Savelberg et al., 2007) to maintain gait function. Additional testing of the relative roles of the hip and ankle in functional movements is needed to assess whether there is a fundamental change in motor control in people with MS. Overall, evidence from this study suggests that walking and balance function in people with MS is dependent on the ability to appropriately coordinate movement at the hip.

2.4.4 Clinical Implications

This work suggests that therapeutic interventions that improve hip coordination will likely have the greatest implications for functional movement. In general, leg

resistance training is effective for improving function in MS. In people with walking impairments, resistance training focused on improving lower limb strength (Broekmans et al., 2013) or eccentric resistance training (Clark and Patten, 2013) are associated with improvements in strength, mobility, ambulation (White et al., 2004), and balance in different clinical populations (Hayes et al., 2011). Specific exercise programs, including cycling, progressive resistance training (Cakt et al., 2010) and lower extremity progressive resistance training (Dalgas et al., 2009; Dodd et al., 2011; Eftekhari et al., 2012), appear to improve muscle strength, balance and fatigue in patients with MS. These exercises are effective in people with MS who have had a recent onset of gait impairment (Motl et al., 2012b) and those with minimal impairment (Garrett et al., 2012), as well as people with varying disability levels (Filipi et al., 2011). Although improving strength and endurance might improve walking speed in neurologically impaired subjects, it could also be related to a more proficient use of the same impaired movement pattern (Kautz et al., 2005) following extensive training interventions. As the current study shows strong a relationship between hip function and clinical function, resistance training focused on improving control and coordination at the hip might be more beneficial for improving function in people with MS.

In conclusion, we found that MS subjects had a reduced ability to coordinate bilateral movement at the hips and ankles, despite being able to produce similar peak torque amplitude and phasing as compared to the control subjects. This reduced ability to coordinate movement was reflected by the negative work ratio. The negative work ratio at the hip was more strongly correlated to clinical measures of function than the ankle, indicating that there is a shift in motor control towards the hip in people with MS.

CHAPTER 3

Decreased Ankle Contribution during Overground Walking in Multiple Sclerosis

3.1 INTRODUCTION

An improved understanding of the mechanisms underlying impairments to walking in people with MS might improve the design and development of new therapeutic regimens. Deficits like muscle fatigue, reduced joint torque, joint torque asymmetries, and gait asymmetries can be detected at early stage MS during regular gait (Kalron et al., 2011a) and dual task gait (Kalron et al., 2010), and are correlated to clinical scores of MS impairment, such as the EDSS (Huisinga et al., 2012a). Even in the absence of clinical signs of pyramidal dysfunction, abnormalities in gait parameters including reduced speed, decreased stride length, and prolonged double support are evident in people with MS (Martin et al., 2006). Thus, investigating how these measured differences in gait parameters relate to functional impairments at various levels of disease progression is important in understanding gait dysfunction in people with MS.

In people with MS, lower extremity weakness resulting from corticospinal tract pathology or general deconditioning is a major cause of poor gait function and reduced efficiency in walking (Thoumie et al., 2005). This weakness is a result of an alteration of the inherent characteristics of skeletal muscle fibers and skeletal muscles (Kent-Braun et al., 1997), and is also related to central activation impairment (Ng et al., 2004). Plantarflexor weakness in particular has been identified as a limiting factor of gait speed in populations with varying neurological impairment (Mueller et al., 1995; Nadeau et al., 1999; Milot et al., 2008). In most cases of neurological impairment, spasticity is often present together with weakness and can be the primary cause of disability (Young, 1994).

Usually, enhanced stretch reflexes resulting in premature activation of the gastrocnemius during lengthening in the stance phase, as well as insufficient muscle activation or excessive coactivation of several muscles, cause reduced walking function (Knutsson and Richards, 1979). In people with MS who are ambulatory but have lower limb impairment, the passive mechanical properties of the gastrocnemius muscles are normal (Hoang et al., 2009). However, MS patients with spasticity have increased phasic EMG response during ankle extensor stretch (Toft et al., 1993), and increased non-reflex stiffness (Sinkjaer et al., 1993). This impaired modulation of the stretch reflex along with increased ankle joint stiffness contributes to the impaired walking ability in MS patients (Sinkjaer et al., 1996b). These lower extremity impairments could result in a redistribution of hip and ankle torques (Lewis and Ferris, 2008) to maintain a viable level of gait function. Hence, comparing ankle and hip torque generation during stance and pushoff will provide insight into the strategies of maintaining gait function despite lower extremity impairment.

In MS, there is often a loss of balance function, that can lead to impaired walking ability and reduced mobility (Frzovic et al., 2000; Heesen et al., 2008; Remelius et al., 2008). Advancing disease status, gait asymmetry, leg flexor-extensor weakness, visually dependent sway, decreased walking endurance and coordination (Sosnoff et al., 2011), and greater trunk angular range of motion exacerbating center of mass movement (Spain et al., 2012) contribute to balance dysfunction and are strong predictors of falls in MS (Kasser et al., 2011). The typical response to reduced balance during walking in MS subjects is to utilize walking strategies that favor slower walking speeds, reduced proximity to stability boundaries (Remelius et al., 2008), and longer double support even at speeds comparable to healthy control subjects (Remelius et al., 2012). Slower walking

speeds and reduced daily ambulatory activity are strongly related to gait and balance measures (Cavanaugh et al., 2011), and could reduce community activity and quality of life in people with MS. There has been increasing evidence that an increased reliance on the hip occurs in MS (Thoumie, 2002), stroke survivors (Jonkers et al., 2009), and the elderly (DeVita and Hortobagyi, 2000; Savelberg et al., 2007) to maintain gait function. Thus, relating gait parameters to balance measures at the hip and ankle will improve the understanding of the effects of balance impairment on compensatory strategies during walking.

In the current study, we recorded kinematic and kinetic data during a short walking task at self-selected speed in MS participants. The participants were instructed to walk a distance of 10m without any assistance at their own comfortable speed. The data from the MS participants was compared to neurologically intact subjects completing the same task. We hypothesized that the amount of ankle contribution, specifically the ankle plantarflexion moments during late stance would be reduced in the MS participants, compared to the healthy control subjects. Furthermore, gait performance would be correlated to the functional ability and clinical scores of the MS participants.

3.2 METHODS

3.2.1a Study Participants

Ten subjects with MS (age range: 38-57 yrs, mean age: 50.6 yrs) participated in this study. All MS participants were community ambulators capable of walking 10 m independently without assistive devices. At the time of the study, three of the ten subjects were taking medication to improve their walking (Ampyra; Acorda Therapeutics, Inc., Ardsley NY) and antispastic medication (Baclofen) to reduce the frequency and intensity of spasms. The clinical features of each subject are described in Table 3-1. Additionally, ten participants (age range: 43-57 yrs, mean age: 51.5 yrs) with no reported neurological damage were recruited for this study as control subjects. Exclusion criteria for this study included: significant cardiovascular problems, respiratory failure, major orthopedic problems including contracture of limbs, joint replacements, significant medical comorbidity, concurrent illnesses limiting the capacity to conform to study requirements, or the inability to give informed consent. Informed consent was obtained prior to study participation and all procedures were conducted in accordance with the Helsinki Declaration of 1975 and approved by the Institutional Review Boards of Marquette University and the Medical College of Wisconsin.

3.2.1b Clinical Assessment

A variety of clinical tests were used to evaluate each MS subject's function and ability to participate in the study. Manual Muscle Testing (MMT) was used to evaluate the muscle strength of MS subjects to establish general motor function under volitional effort. Scores were given between 0 (no perceivable muscle contractile activity) and 5

(limb position was maintained with full resistance through complete joint range of motion). Half scores (+, -) were given to graded muscles (Kendall, 1983). The Modified Ashworth Scale (MAS) was used to measure the muscle hypertonia of the MS subjects (Bohannon and Smith, 1987). The subjects' limb segments were moved through a range of motion and the muscle tone in each segment was graded between 0 (no increase in muscle tone during movement) and 4 (large amount of rigidity in flexion or extension during movement) (Table 3-2). The Berg Balance Scale (BBS) was used to evaluate the balance function in MS subjects (Berg et al., 1992). The MS subjects were scored on a 0-4 scale while performing several tasks involving sitting, standing, reaching, and turning, with 0 requiring the most assistance and 4 requiring no assistance while performing the task. The 25 feet walk test (25FWT) was used to evaluate the walking ability of the MS subjects (Kaufman et al., 2000). The MS subjects were required to walk 25 feet repeated in three trials at their own comfortable speed, and the time required was recorded and averaged. The Fatigue Severity Scale (FSS) was a 9-question questionnaire that allowed each subject to rate his level of fatigue between 1 (strong disagreement with the statement) and 7 (strong agreement with the statement), with a typical score of 4 and above indicating that fatigue was a significant factor of the subject's daily activities (Krupp et al., 1989). The Symbol Digit Modalities Test (SDMT) was used to evaluate the cognitive function of the MS subjects (Lewandowski, 1984). The SDMT is a simple substitution task where the subject has to use a reference key to pair specific numbers with given geometric figures within 90 seconds, and the total number of right answers is the score of cognitive abilities. The 9 hole peg test (9HPT) was used to evaluate the coordination function of the MS subjects (Goodkin et al., 1988). The subject was required

to place nine pegs into nine holes on a small platform in front of them, and then remove each peg one by one as quickly and accurately as possible. The test was repeated twice for each hand, and the time required for each iteration was recorded. All clinical tests were completed by a licensed physical therapist prior to beginning the experiment.

Subject specific information is provided in Tables 3-2 and 3-3.

Table 3-1 Clinical Features of MS Subjects

Subject	Age (yrs)	Years with MS	9HPT (s)	SDMT	FSS (of 7)	BBS (of 56)	25FWT (s)	Medications
S01	49	27	22.77	30	6.56	40	11.17	Ampyra, Copaxone
S02	52	15	28.65	40	6.00	46	9.32	Tysabri
S03	56	30	24.98	39	5.11	29	14.71	Baclofen, Ampyra, Interferon Beta, Amantadine
S04	48	8	17.64	50	4.50	55	6.94	Interferon Beta
S05	47	11	24.35	33	5.11	40	12.79	
S06	59	10	18.73	53	4.11	56	7.33	Tysabri
S07	50	5	21.65	48	4.44	47	6.51	Baclofen
S08	38	2	21.30	46	4.67	56	6.52	Baclofen, Ampyra
S09	57	6	27.35	37	4.78	35	18.40	
S10	50	3	20.52	44	4.67	52	7.62	

Table 3-2 Manual Muscle Test Scores of MS Subjects

Subject	Hip Abductors		Hip Flexors		Hip Extensors		Knee Flexors		Knee Extensors		Ankle Dorsiflexors		Ankle Plantarflexors	
	L	R	L	R	L	R	L	R	L	R	L	R	L	R
S01	4	4	4	4	4	4	5	4	4	4	4	4	4	4
S02	4	4	4	4	4	4	2+	5	3+	5	2	5	4	5
S03	4	3	5	5	5	3+	5	5	5	5	5	2+	5	3
S04	4	4	4+	4+	5	5	5	5	5	5	5	5	5	5
S05	4	4	4	4	5	5	4	4	5	5	5	5	5	5
S06	5	5	5	5	5	5	5	5	5	5	5	5	5	5
S07	4	5	4	5	4	5	4	5	4	5	4	5	2	5
S08	4	4	4	4	5	5	5	5	5	5	5	5	5	5
S09	3	4	3	4	5	5	3	4	3	3	4	5	2	5
S10	4	5	4	5	5	5	5	5	5	5	5	5	5	5

Table 3-3 Modified Ashworth Scores of MS Subjects

Subject	R Knee Extensors	R Knee Flexors	R Ankle PF	R Ankle DF	L Knee Extensors	L Knee Flexors	L Ankle PF	L Ankle DF
S01	0	0	1	0	1	0	0	0
S02	0	0	0	0	0	1	1	0
S03	0	2	2	0	0	2	2	0
S04	0	1	1	0	0	1	1	0
S05	0	1	1	0	1	1	1	0
S06	0	0	0	0	0	0	0	0
S07	0	0	0	0	0	0	0	0
S08	1	1	1	1	0	0	1	1
S09	0	2	2	0	0	2	0	0
S10	0	0	1	0	0	0	0	0

Plantarflexors (PF) and dorsiflexors (DF) abbreviated

3.2.2 Experimental setup

Study participants were required to walk 10m across a room at self-selected speed without any assistance. Subjects were set up with markers on their lower body (Appendix A Table 6-1). MS subjects wore a safety harness tethered to a rail system on the ceiling to prevent injury in case of falls. Surface EMGs were recorded bilaterally from the vastus medialis (VM), rectus femoris (RF), vastus lateralis (VL), medial hamstrings (MH), medial head of the gastrocnemius (MG), and tibialis anterior (TA) from all subjects. Recording electrodes (Delsys Inc, Boston, MA) were placed on the cleansed, lightly abraded skin over each muscle belly. EMG signals were bandpass filtered (25-450 Hz) prior to sampling at 1000Hz. Kinematic data were recorded via six motion capture cameras (MX3+, Vicon Motion Systems Ltd, Oxford, UK) at 100 Hz, and kinetic data were recorded via the two AMTI OR6-7MA force plates (Advanced Mechanical Technology, Inc, Watertown, MA, USA) at 1000 Hz. All signals were recorded in Vicon Nexus (Vicon Motion Systems Ltd, Oxford, UK).

3.2.3 Experimental Protocol

Subjects started from a standing position, and were cued to start walking 10m across the room at their own comfortable speed. At the end of 10m denoted by markings on the floor, subjects stopped, turned around, and awaited the cue for the next trial. During each trial, the occurrence of full force plate contact – i. e. each leg's heel strike (HS) to toe off (TO) – was noted, and trials were repeated until at least 15 full force plate steps, and 20 full gait cycles (HS to HS) from each leg had been recorded. Subjects were allowed to rest at any time between trials.

3.2.4 Data Analysis

The kinematic and kinetic data was recorded and used for the reconstruction of a subject-specific full body model in Vicon Nexus. Gait events heelstrike and toecoff were manually marked using observations of heel and toe markers, as well as ground reaction forces from the force plates. The model outputs of joint angles and moments, as well as the EMG data and force plate outputs were exported for further processing in MATLAB. All model outputs were low pass filtered at 10 Hz using a 4nd order zero phase Butterworth filter.

To obtain a representative average kinematic profile during gait, each subject's stance and swing phases were separately downsampled and averaged within subjects and groups to obtain the representative average kinematic profile for each subject and for the MS and control groups. Kinematic gait parameters, joint range of motion, and joint moments were then calculated. The peak flexion angles and moments (maximum hip flexion and ankle plantarflexion) of the kinematic profile were identified and used for statistical comparison of kinematics between groups. The sagittal hip and ankle moments were the primary dependent variables used as indicators of the contribution of each joint during walking. Specifically, hip and ankle moments during the push off phase of stance were calculated and used for comparison of relative joint contributions to gait in the MS and control groups. All profiles and parameters were first calculated for the left and right leg of each subject. Data from the left and right leg were averaged together for each subject, then within the group for comparison between the MS and control groups.

A measure of dynamic balance during gait was also estimated. The center of mass (CoM) medial-lateral displacement during gait was approximated by tracking the center

of mass of the pelvis segment in the model. The movement of the pelvis in the medial-lateral direction (pelvic sway) was linearly detrended to account for any drift in direction of the subject. The approximate CoM medial-lateral displacement was used as a performance measure of dynamic balance during walking.

EMG signals were used as an indication of the level of specific muscle activity during walking. All surface EMG recordings were notch filtered at 58 - 62 Hz to remove line noise and bandpass filtered at 30-200 Hz using 4nd order zero phase Butterworth filters (MATLAB; the Mathworks Inc., Natick, MA). For analysis, the EMG data were rectified and low pass filtered at 5 Hz using a 4th order zero-phase Butterworth filter to obtain the envelope, and then ensemble averaged across cycles within each subject and trial. The signals from the MG and TA were used to determine the differences in the pattern of ankle activity between MS and control subjects during walking.

3.2.5 Statistical Analysis

To investigate the difference in gait characteristics and joint contribution during gait between MS and control subjects, the gait parameters (walking speed, cadence, stride length, step length, double support, pelvic sway range) and kinematics (peak joint moments and angles) at the hip and ankle were separately compared at each joint between groups using a one way ANOVA (SPSS Inc., Chicago IL). Significance was accepted at $p < 0.05$. To understand how balance affects walking ability as well as how the joint kinematics during gait relate to clinical measures of walking, linear regression was used to compare the clinical measures of BBS, 25FWT, gait kinematics, and gait parameters.

3.3 RESULTS

3.3.1 Hip and Ankle Contribution

In this study, we wanted to determine if the difference in walking ability between MS and healthy control subjects could be attributed to a reduced ability to generate appropriate joint torque for pushoff. Specifically, we analyzed gait parameters and compared the sagittal flexion moments at the hip and ankle during late stance, to determine if the deficit in walking function could be related to abnormal joint contribution during the stance phase of gait.

The representative single subject kinetic and kinematic data (one MS and one control subject) during the stance phase (from HS to TO) suggested similar overall gait patterns in both subjects (Figure 3-1). The hip and ankle range of motion was similar between subjects, with the MS subject having reduced dorsiflexion and increased plantarflexion at the ankle. Hip flexion and ankle plantarflexion moments were lower in the MS subject. Furthermore, the rise in plantarflexion moment from early to late stance in the MS subject followed a more linear slope, unlike the kinematic profile of the control subject.

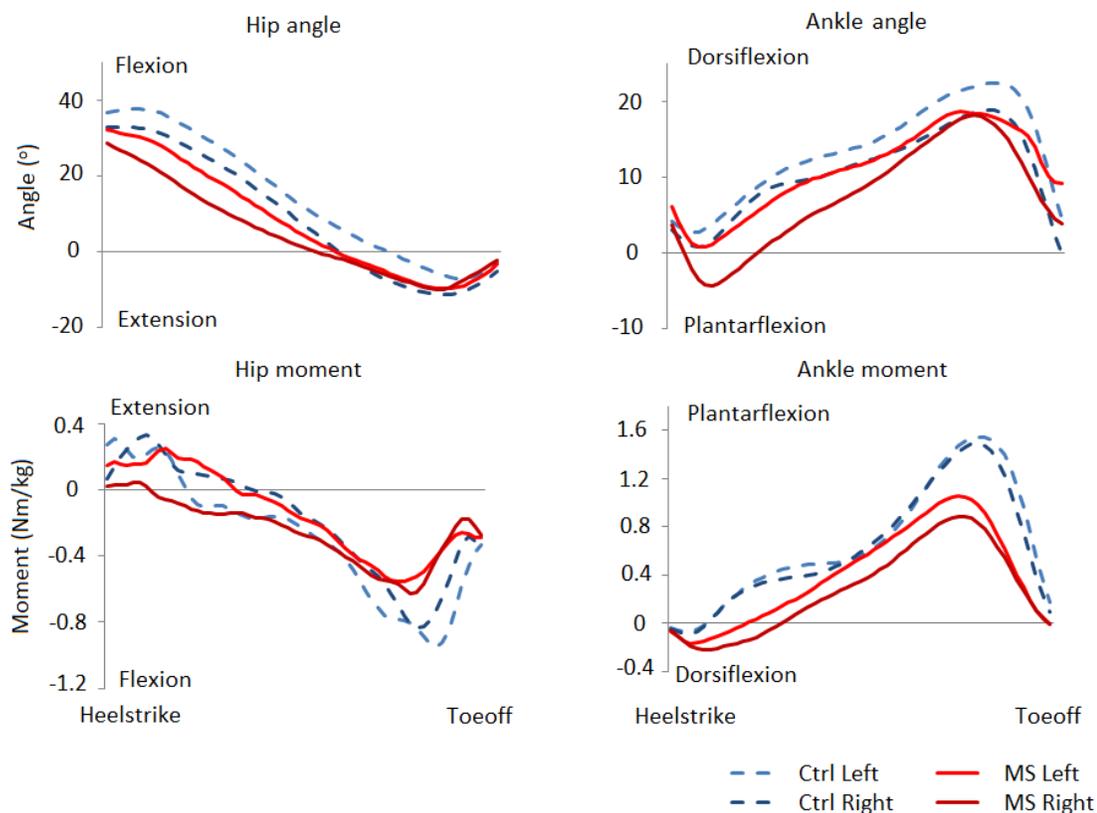


Fig 3-1 Representative Single Subject Data. MS (solid line) and control (dashed line) subject's left and right leg joint kinematics during stance. Each plot represents subject stance from heelstrike to toeoff on a force plate during walking. The MS subject was observed to have decreased hip and ankle peak moments during stance, compared to the control subject.

The group gait profiles during stance were generally similar between the MS and control group, with observable differences in peak moments and plantarflexor modulation. Inspection of the group averaged kinematic profiles (Figure 3-2) showed that the MS subjects had a slightly reduced hip extension angle, and a lower peak hip flexion moment, occurring late in stance. At the ankles, the MS group sustained a larger ankle dorsiflexion angle throughout stance. They also showed a linear rise in plantarflexion moment and had a lower peak plantarflexion moment late in stance compared to the control group. Comparison of the group peak hip and ankle flexion moments (Figure 3-3) between the MS and control group showed slightly decreased peak moments in both

joints for the MS group, which was significantly different at the ankles (one way ANOVA $p < 0.05$). The peak extension moments showed no significant difference at the hip ($p = 0.797$). The range of motion showed no significant differences at the hip ($p = 0.357$) and ankle ($p = 0.110$). The peak to peak values of the joint moments showed no significance at the hip ($p = 0.448$), but approached significance at the ankle ($p = 0.052$).

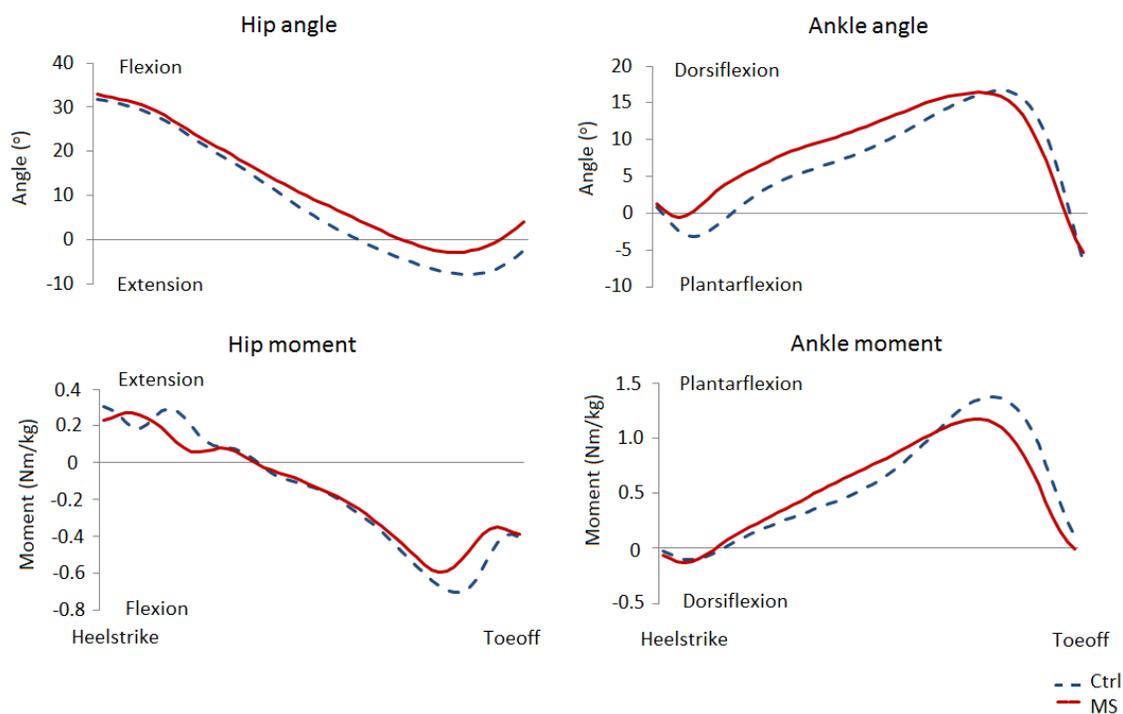


Fig 3-2 Group Averaged Kinematic Plots. MS (solid line) and control (dashed line) group averaged joint kinematics (left and right leg averaged) during stance. Each plot represents subject stance from heelstrike to toeoff on a force plate during walking. The MS group produced a smaller peak plantarflexion moment during stance, compared to the control group.

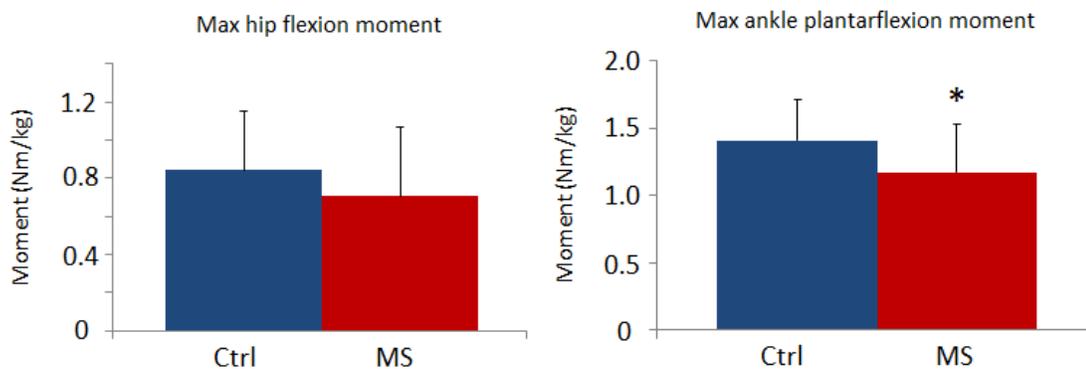


Fig 3-3 Peak Joint Flexion Moments During Stance. The MS group produced lower flexion moments at the hip ($p=0.384$) and ankle ($p = 0.019$) compared to the control group. Standard deviation bars are indicated.

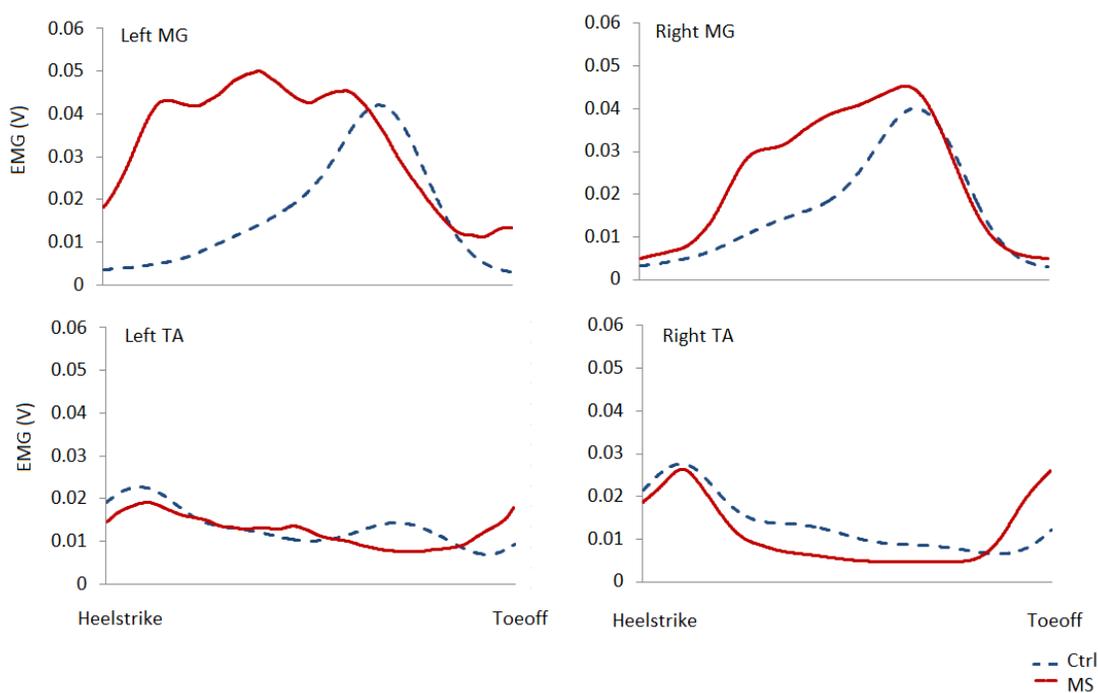


Fig 3-4 Group Averaged EMG. Control (solid line) and MS (dashed line) MG and TA EMG during stance. The MS group demonstrated impaired MG EMG modulation, and a slightly lower TA EMG activity level than the control group.

The muscle activity at the ankle in the MS group was noticeably different from the control group during stance. Inspection of group averaged EMG data showed that the MS group had difficulty in MG modulation, noted by an early, sustained activation of the MG, compared to the low rise in EMG early in stance, followed by a peak in late stance

and early pushoff in the control group. However, the peak MG EMG activation levels were similar for both groups. The TA activity in both groups was generally low during stance, with similar profiles and the MS group having slightly lower activity than the control group.

3.3.2 Interaction Between Balance and Walking

The MS group showed a significant difference in gait parameters consistent with impaired walking function as compared to the control group, including reduced walking speed, stride length, step length, and increased double support (Table 3-1). The range of pelvic sway was larger in the MS group, while the ankle angle ROM was decreased during swing.

Table 3-4 Participant Gait Parameters

	Controls	MS	p
Walking speed (m/s)	1.08±0.11	0.78±0.41	.035*
Cadence (steps/min)	108.42±7.35	96.92±33.01	.298
Stride length (m)	1.20±0.07	0.91±0.36	.025*
Step length (m)	0.60±0.03	0.47±0.17	.040*
Double support (% gait cycle)	23.96±33.68	39.07±19.28	.025*
Pelvic sway range(mm)	29.94±6.63	48.15±32.36	.104
Swing hip angle ROM	31.40±3.80	25.16±12.19	.140
Swing ankle angle ROM	20.54±6.50	13.85±7.44	.046*

Values are ±SD. Significance (p<0.05) is indicated with a *.

The clinical measures of 25FWT and BBS were correlated with each other ($R^2=0.771$ p=0.001), and the MS group gait parameters of double support, walking speed, and pelvic sway were also correlated with each other. The MS group showed a greater double support (percent gait cycle) with greater impairment, denoted by higher 25FWT, lower BBS, and slower walking speed (Figure 3-5). The range of pelvic sway was also

correlated to impairment, denoted by greater double support, and decreased walking speed (Figure 3-6). The control group maintained a high walking speed that was consistent with a low double support. Due to the much smaller range of walking speed in the control group, no trend relating walking speed to gait parameters could be determined.

The clinical measures of BBS and 25FWT followed a consistent trend when compared to measures of joint moment during walking. The MS subjects showed an increase in peak hip and ankle moments with increasing BBS score and decreasing 25FWT score (Figure 3-7). The peak hip moment showed a significant correlation to the 25FWT ($R^2=0.465$, $p=0.030$). The correlation between peak ankle moment and BBS approached significance ($R^2=0.337$, $p=0.059$).

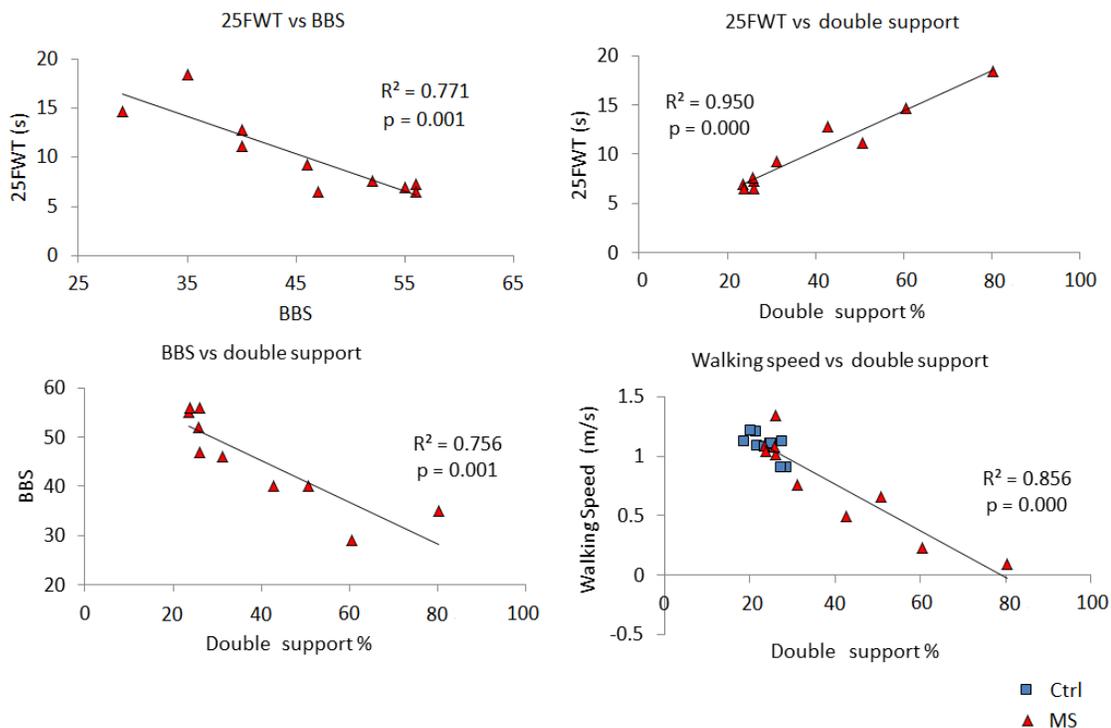


Fig 3-5 Double Support and Clinical Scores Correlations. The regression between 25FWT and BBS showed a strong relationship between clinical measures of impairment in walking and balance. Gait parameters of walking speed and double support also showed a strong trend of decreasing gait performance with increasing clinical impairment.

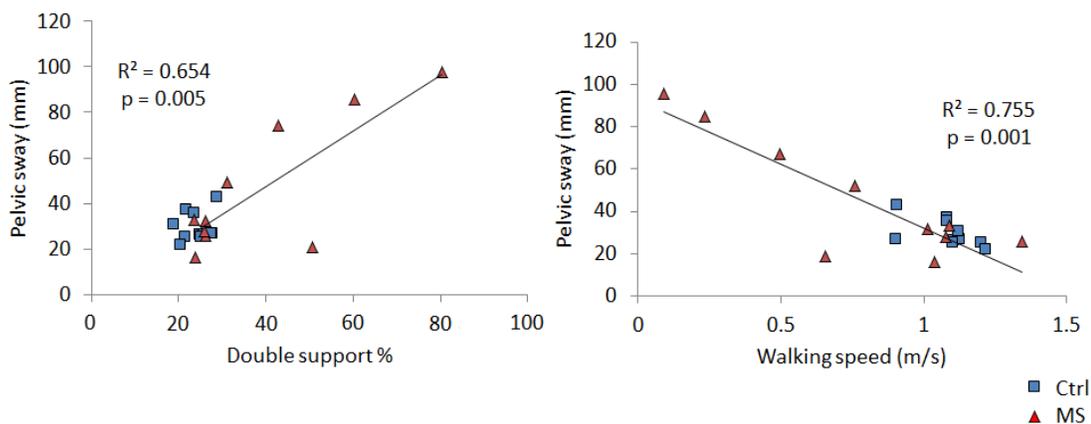


Fig 3-6 Pelvic Sway Correlation to Double support and Walking Speed. Pelvic sway, as an approximation of CoM medial-lateral displacement, showed a strong correlation to double support and walking speed.

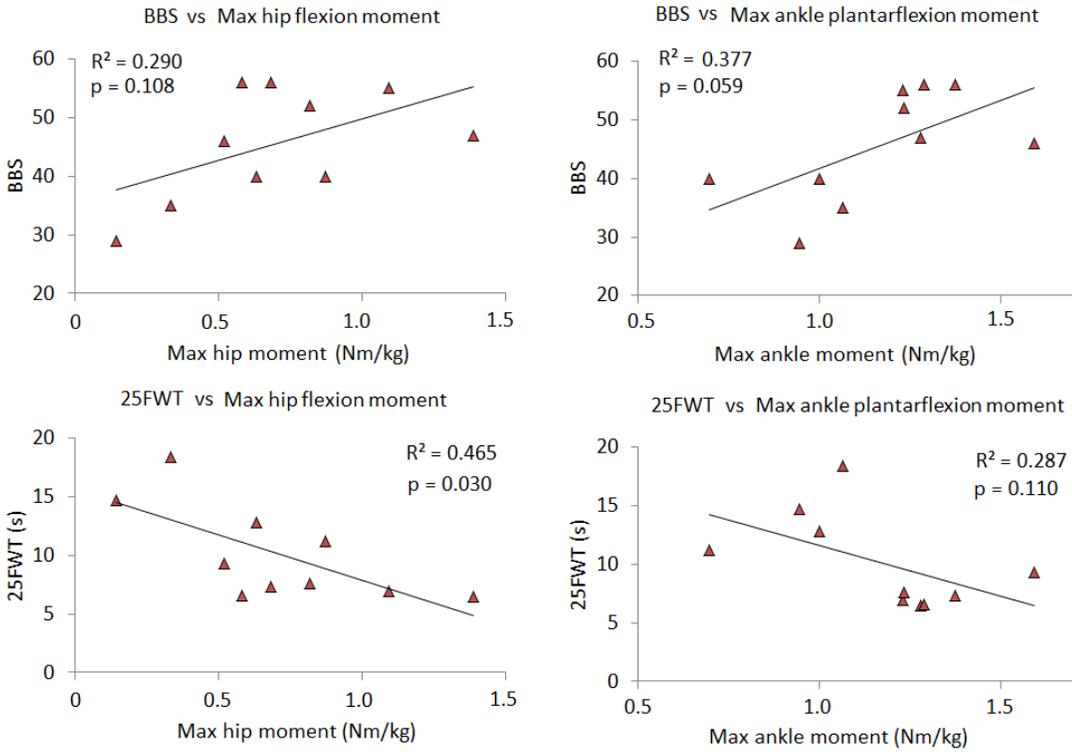


Fig 3-7 Joint Moment and Clinical Score Correlations. Regression between joint moments in the stance phase of gait and BBS and 25FWT showed an increase in joint moments with decreasing impairment. Maximum hip flexion was a good predictor of clinical measure of walking ability ($R^2 = 0.465$, $p = 0.030$).

3.4 DISCUSSION

Results from this study showed that there is a diminished contribution at the ankle in people with MS during overground walking. Although the MS group had a reduced walking speed compared to the control group, both groups showed comparable joint angles and peak hip moments during stance, while the ankle moments were significantly reduced in the MS group, likely related to poor modulation of EMG at the gastrocnemius. MS subjects showed a significantly reduced walking speed, stride length, step length, and double support, compared to control subjects. Increasing double support and decreasing walking speed showed a consistent correlation to increasing impairment measured by the 25FWT and BBS.

3.4.1 Ankle Deficits During Walking

People with MS have a reduced ankle contribution to gait. During overground walking, the MS group was observed to have a significantly reduced peak ankle plantarflexion moment, but comparable joint range of motion and peak hip moments to the control group. Inspection of the kinematic profile during stance showed that this reduction in moment occurred during pushoff. Furthermore, the MS group was observed to have a more spring-like linear rise in ankle moment slightly higher in amplitude than the control group during mid-stance. In contrast, the control group demonstrated modulation of the ankle moments, showing the characteristic net dorsiflexor moment during loading response, net plantarflexor moment during mid-stance, and net plantarflexor moment during pushoff, known respectively as the first, second, and third rocker (Ounpuu, 1994). In the MS group, the second rocker was greatly diminished, and

the third rocker in conjunction with peak ankle plantarflexion moment was reduced. This indicates that there is a deficit in eccentric (second rocker) and concentric (third rocker) force modulation of the plantarflexors in MS. It is possible that the plantarflexion torque production during midstance is dominated by passive stretch of the gastrocnemius and soleus, resulting in an increase in residual force enhancement (Hisey et al., 2009) similarly seen in elderly (Power et al., 2012), as people with MS often preserve the passive mechanical properties of the gastrocnemius (Hoang et al., 2009) and have increased non-reflex stiffness (Sinkjaer et al., 1993). With the loss of volitional strength and control at the ankle, people with MS might establish spring-like behavior during the progression stage of the stance phase of gait, which might be sufficient to approximate the behavior of the healthy ankle in slow to preferred walking speeds and low load weights (Shamaei et al., 2011). This indicates that people with MS might utilize a strategy that diminishes the importance of the ankle as a primary torque generator during gait.

The reduced ankle contribution to gait seen in people with MS might be attributed to inappropriate ankle muscle activity while walking. Inspection of the EMG showed that the MS group produced early sustained activity at the gastrocnemius which might be caused by poor reflex modulation and spasticity (Sinkjaer et al., 1995) similarly seen during repeated ankle stretches in spinal cord injury (Hornby et al., 2006). Conversely, early gastrocnemius contraction might also be a strategy to interrupt the normal stretch induced losses in active and passive plantarflexor joint moment and neuromuscular activity (Kay and Blazevich, 2009) during stretching of the soleus in mid-stance.

Nonetheless, there is clearly poor modulation of the gastrocnemius EMG of the MS subjects, which likely contributes to inefficient torque generation at the ankle during gait.

3.4.2 Interaction Between Balance and Walking

Balance and walking function are highly correlated in people with MS, and the reduction in ankle contribution to gait likely results in the hip determining walking function. In the current study, people with MS demonstrated a clinical relationship between their ability to maintain balance and their walking function, as seen by the strong correlation between the BBS and 25FWT. The clinical measures also showed good regressions to measures of gait performance such as walking speed, double support, and pelvic sway, reiterating the importance of balance function to walking ability. The ability to generate torques at the hip and ankle was related to functional impairment, observed by decreasing hip and ankle peak flexion moments with increasing impairment measured by the 25FWT and BBS. This indicates that torque generation at the hip and ankle are essential for optimal walking function. Furthermore, the maximum hip flexion moment was a strong predictor of clinical measures of walking function, alluding to the increased reliance on the hip and subsequently reduced reliance on the ankle to maintain walking performance in MS.

A comparison of walking pattern between MS and control subjects could not be clearly established due to differences in self-selected walking speed. Initially, double support and pelvic sway were calculated as measures of dynamic balance during walking. Double support was observed to have a strong correlation with increasing impairment and decreasing walking speed, which was consistent with previous studies that showed that people with MS had slower preferred speeds with longer double support, and longer

double support during fixed speed comparisons to controls (Remelius et al., 2012). However, the results and trends found for the MS group could not be directly compared to the control group, as double support typically decreases with increasing walking speed (Lemke et al., date unknown; Nilsson et al., 1985; Bilney et al., 2003; Saremi et al., 2006; Dubbeldam et al., 2010), and both groups in this study were not speed matched, so as to obtain walking speed as a primary outcome. Similarly, pelvic sway, as an estimation to the medial-lateral center of mass movement, and measure of dynamic balance during gait, displayed a strong correlation with increasing impairment and decreasing walking speed, but has been shown to be dependent on walking speed (Remelius et al., 2012). This trend of increasing pelvic sway with decreasing walking speed might reflect the increasing dynamic instability and reduced walking speed that accompanies increasing impairment, with MS subjects adopting a change in gait strategy that favored reduced walking speed and reduced proximity to stability boundaries (Remelius et al., 2008). This inability to effectively coordinate the center of mass might be indicative of a failure to efficiently utilize passive elastic energy mechanisms, resulting in increased reliance on active work generation to sustain gait (Wurdeman et al., 2012). Overall, the MS group selected a preferred speed that resulted in significantly reduced walking speed, stride length, step length, and double support, compared to control subjects. This difference in gait parameters is consistent with literature and has been shown to be detected in patients in the absence of clinical signs of pyramidal dysfunction (Martin et al., 2006), patients with relatively short disease duration during normal gait and dual task gait (Kalron et al., 2010), and are correlated with the associated neurological disability (Givon et al., 2009). Hence, it is likely that balance function limits walking ability in people with MS, which

causes people with MS to adjust their walking speed preferences according to impairment.

3.4.3 Change in Hip and Ankle Strategy During Walking

It is likely that people with MS utilize an increased hip strategy to maintain gait performance. To maintain a functioning level of ambulation to accommodate for gait variability, muscular impairments, or weakness, the joint contributions in the legs have to change to produce optimal synergy for walking. Changes at the ankle like increasing plantarflexor peak torque and limiting dorsiflexion ROM may help decrease gait deviations such as decrease step length and walking speed (Mueller et al., 1995). In the case of people with MS experiencing ankle weakness or a decreased ability to modulate ankle activity, increasing plantarflexor torque might not be a viable solution to improving gait. Plantarflexor muscular utilization ratio is typically higher than the hip during walking, but the hip reaches similar values to the ankle at higher gait cadences (Requiao et al., 2005). In the current study, the MS subjects might have selected a preferred lower gait speed which allowed them to work within their comfortable range of ankle plantarflexor contribution during walking. The inability to modulate ankle muscle activity like premature recruitment of the gastrocnemius despite achieving similar amplitudes of EMG activity, may be related to the lower peak ankle moments compared to the control subjects and resulted in abnormal gait parameters (Benedetti et al., 1999). Furthermore, the peak hip flexion and extension moments were not significantly different between the MS and control group, despite the significantly lower walking speed in the MS group. This gives an indication that the MS subjects altered their joint contribution

towards the hip, producing an increased hip contribution and decreased ankle contribution, while achieving a slower gait speed than the control group.

A change in gait strategy is necessary in people with MS due to varying levels of impairment at the hip and ankle. Altering the joint contribution strategy either towards the ankle to compensate for hip weakness (Lewis and Ferris, 2008), or towards the hip to compensate for plantarflexor weakness (Nadeau et al, 1999), has been shown to be useful in overcoming limitations in gait, particularly in people with neurological deficits. Several studies involving the elderly have shown that a redistribution of joint torques from plantarflexion to hip extension occurs more so in active than inactive elderly (Savelberg et al., 2007), and also while walking at the same speed as young adults (DeVita and Hortobagyi, 2000), making hip extension torque a significant independent predictor for free walking velocity, stride length, and cadence (Burnfield et al., 2000). Patients with MS and sensory loss have also been shown to produce a higher contribution of both flexors and extensors of the lower limbs to maintain gait speed, exhibiting a correlation between gait speed and muscle strength (Thoumie, 2002). Although the redistribution of torques might be a viable strategy to maintain gait function, impaired ankle power generation combined with saturation of hip power generation would still limit the potential to increase walking speed (Jonkers et al., 2009). As the MS disease progression increasingly impairs gait function, the reliance on hamstring and quadriceps strength to maintain gait speed might increase (Thoumie et al., 2005), forcing a change in gait strategy that is consistent with disease progression and increasing levels of impairment.

3.4.4 Clinical Implications

The ability to accurately and meaningfully identify points of weakness in a person's gait and identify methods of rehabilitation to improve gait performance is important in improving the quality of life in people with neurological impairment. In people with MS, the 6 minute walk test (6MWT) or 25FWT are the most common clinical tests used to evaluate walking function. The 6MWT has been correlated to subjective measures of ambulation and physical fatigue (Goldman et al., 2008), while an increase above 20% in variation in the 25FWT has been linked to significant changes in gait (Kaufman et al., 2000), showing that there is strong merit in using these clinical tests for assessment of walking in MS. These clinical tests of walking ability have been used together with the EDSS to relate advancing disease status to other measures of balance like limits of stability, sway, gait asymmetries, and leg strength, to better predict falls in people with MS (Kasser et al., 2011). By further understanding specifically how the hip and ankle contributions change and correlate to these clinical measures, appropriate rehabilitative measures can be taken to focus on joint strengthening and improve walking function.

Endurance and resistance exercises targeting whole leg or specific joints might be useful in improving walking function in people with MS. Endurance knee extensor strength and isometric knee flexor strength have been shown to be a good main predictor of walking capacity (Broekmans et al., 2013), and increases in plantarflexor and hip flexor strength after a training exercise intervention in hemiparetic participants showed reduction in levels of effort during walking (Milot et al., 2008). Furthermore, levels of effort during walking has been inversely associated with gait speed, stride length, and

positively associated with double support in people with mild MS (Motl et al., 2012a). These findings indicate that changes to strength at the hip and ankle have the potential to cause changes to walking function in people with MS.

Physical and functional limitations relating to the stage of disease progression in people with MS might limit the nature and intensity of the physical rehabilitation, requiring a variety of rehabilitation approaches for best results. Endurance exercises (Dettmers et al., 2009) and resistance training (Gutierrez et al., 2005) have been shown to be effective intervention strategies for improving walking and functional ability in people with MS. Treadmill exercises have been shown to reduce energy cost of walking and reduce sway in people with MS (Benedetti et al., 2009), while elliptical exercises have been shown to alter joint torques and power at the hip and ankle in people with MS closer to that of healthy young adults (Huisinga et al., 2012b). In lower functioning MS participants with greater difficulty in walking, robot-assisted interventions might provide a good starting point for rehabilitation. In previous studies typically involving weight supported locomotor training or a Lokomat (assistive gait robot), improvements in functional mobility parameters (Giesser et al., 2007) have reinforced the feasibility of robot assisted gait training in people with severe walking disabilities (Beer et al., 2008), and has the potential to reduce gait impairment in MS (Lo and Triche, 2008). One caveat that exists in using robot assisted gait training or rehabilitative methods that attempt to alter the MS subject's gait strategy to resemble that of a healthy control, is that given the physical and functional limitations of the person with MS, the optimal gait strategy might be one that deviates from a healthy control. For example, with the Lokomat guiding the subject through physiologically symmetric gait patterns, abnormal asymmetric joint

torque patterns, characteristic of the neurological impairment, were still found in stroke subjects (Neckel et al., 2008). Balance strategies during gait might also be task specific, and vary with age (Shkuratova et al., 2004), disease type, and disease progression. Hence, creating and applying the best rehabilitative method for improving gait function in people with MS might involve specific targeting of the hip and ankle, but also require multiple approaches depending on disease progression and physical limitations.

In conclusion, we found that MS subjects had a diminished contribution at the ankle during stance, likely due to the inability to modulate ankle torque and muscle activity. The strong correlation between clinical measures of balance and walking function highlights the importance of balance function during walking. Additionally, the relationship between reduced joint moments and decreasing walking function reiterates the importance of appropriate torque production during walking. Furthermore, the hip moments being a good predictor of walking function indicates the use of a hip strategy in MS. Overall, it is likely that people with MS adopted an increased hip strategy that reduced the importance of ankle contribution to gait due to impairments at the ankle.

CHAPTER 4

Increased Hip Versus Ankle Contributions to Standing during Arm Tracking Movements in Multiple Sclerosis

4.1 INTRODUCTION

An improved understanding of the contributions of the ankle and hip to standing balance in people with multiple sclerosis (MS) is potentially important for improving balance control and preventing falls. Balance impairments affect up to 82% of the MS population (Martyn and Gale, 1997), resulting in an increase in the number of falls (Cattaneo et al., 2002b; Soyuer et al., 2006; Nilsagård et al., 2009; Matsuda et al., 2011; Prosperini et al., 2011; Sosnoff et al., 2011; Coote et al., 2012), even in the early stages of MS (Moen et al., 2011). The roles of the ankle and hip in balance control are interesting because two distinct strategies for maintaining balance, namely the ankle strategy and the hip strategy, have been proposed (Nashner and McCollum, 1985). These strategies might be used separately or together in varying degrees to produce optimal and adaptable balance control, depending on the difficulty of the balance task (Gatev et al., 1999; Runge et al., 1999; Hwang et al., 2009). Given the high incidence of falls, a better understanding of the relative contributions of the ankle and hip to standing balance in people with MS would provide insight into balance control problems and could aid in the planning of therapies to improve balance control.

Deficits in balance control has been speculated to stem from impaired sensory feedback and integration (Dietz, 1992; Horak et al., 1997) or other motor impairments such as spasticity (Rougier 2007). Till date, sensorimotor impairments such as impaired reflexes, spasticity, co-contraction (Toft et al., 1993; Crone et al., 1994; Sinkjaer et al.,

1999; Morita et al., 2001), muscle fatigue, and torque asymmetries (Kalron et al., 2011a), have been largely documented at the ankle. People with MS often have problems with ankle spasticity (Rizzo et al., 2004) that likely complicates balance control, since the ability to modulate ankle stiffness is an important component of the control of standing balance (Gatev 1999). Individuals with MS show a correlation between level of spasticity, sway velocity, and amplitude of the soleus H-reflex (Sosnoff 2010). Hence, it is likely that impaired control at the ankle causes problems in the control of standing balance in people with MS, and balance performance must either be compromised, or a compensatory strategy, possibly involving hip control, is used to maintain balance.

Responding to an external perturbation requires strategies for movement, and execution of these strategies using muscle synergies and joint torques. These strategies are limited by external constraints imposed by the environment and task, and internal constraints imposed by the individual's biomechanical system (restricted joint range of motion, strength) and nervous system (accuracy of sensory information, force and position control mechanisms) (Horak, 1996). Sensory impairments or delays in postural responses due to slowed sensory or motor conduction (Inglis et al., 1994), slowed spinal conduction (Pratt et al., 1992), or a delay in central processing (Shumway-Cook and Woollacott, 1985; Woollacott et al., 1986) can cause changes to strategies and movement. Sensory deficits such as a loss of proprioception or abnormal spatiotemporal coordination of automatic postural responses can cause reversals in the normal distal-to-proximal temporal sequencing of postural muscle activation, resulting in a decreased reliance on the ankle and an increased reliance on the hip for balance correction (Nashner et al., 1983; Di Fabio et al., 1990).

Testing of balance control typically involves a perturbation (internal or external) with measurements of joint kinematics (range of motion) and kinetics (moment) to quantify the ensuing corrections. To identify the relative contribution of the hip and ankle joints to standing balance, external perturbations to a standing platform are most commonly applied (Horak et al., 1997). Several studies have addressed the effect of an external perturbation below or at the feet to examine the role of joint strategies in balance (e.g. Kuo and Zajac, 1993; Laessoe and Voigt, 2008; Terry et al., 2011). The use of internal perturbations, such as arm movements, is somewhat less common, and includes anticipatory balance control to account for the planned limb movement. Examining the effects of functional reach on balance control is important, as leg responses during reach not only stabilize the body but also initiate and assist whole-body reaching (Kaminski and Simpkins, 2001). Often, people with MS are able to maintain balance in steady stance, but perform poorly when the balance task difficulty increases or during an internal perturbation like a functional reach (Frzovic et al., 2000). Thus, a benefit of identifying balance strategies during arm movement is that it closely models an important aspect of integrated functional movement.

In the current study, we recorded ankle and hip kinematic and kinetic data during a standing, arm tracking task. Data from participants with MS were compared to neurologically intact subjects completing the same tasks. We hypothesized that the amount of hip relative to ankle contribution to standing balance, specifically the joint moments and range of motion (ROM), would increase to a greater extent in MS participants as the tracking speed increased compared to the healthy controls.

4.2 METHODS

4.2.1a Study Participants

Nine subjects with MS (age range: 38-57 yrs, mean age: 51 yrs) participated in this study. All MS participants were community ambulators capable of walking 10 m and standing independently without assistive devices for up to one minute. At the time of this study, three of the nine subjects were taking medication (Ampyra; Acorda Therapeutics, Inc., Ardsley NY) to improve their walking and antispastic medication (baclofen) to reduce the frequency and intensity of spasms. The clinical features of each subject are described in Table 4-1. Additionally, nine participants (age range: 43-57 yrs, mean age: 51.8 yrs) with no reported neurological damage were recruited for this study as control subjects. Exclusion criteria for this study included: significant cardiovascular problems, respiratory failure, major orthopedic problems including contracture of limbs, joint replacements, significant medical co-morbidity, concurrent illnesses limiting the capacity to conform to study requirements, or the inability to give informed consent. Informed consent was obtained prior to study participation and all procedures were conducted in accordance with the Helsinki Declaration of 1975 and approved by the Institutional Review Board of Marquette University and the Medical College of Wisconsin.

4.2.1b Clinical Assessment

A variety of clinical tests were used to evaluate each MS subject's function and ability to participate in the study. Manual Muscle Testing (MMT) was used to evaluate the muscle strength of MS subjects to establish general motor function under volitional effort. Scores were given between 0 (no perceivable muscle contractile

activity) and 5 (limb position was maintained with full resistance through complete joint range of motion). Half scores (+, -) were given to graded muscles (Kendall, 1983). The Modified Ashworth Scale (MAS) was used to measure the muscle hypertonia of the MS subjects (Bohannon and Smith, 1987). The subjects' limb segments were moved through a range of motion and the muscle tone in each segment was graded between 0 (no increase in muscle tone during movement) and 4 (large amount of rigidity in flexion or extension during movement) (Table 4-2). The Berg Balance Scale (BBS) was used to evaluate the balance function in MS subjects (Berg et al., 1992). The MS subjects were scored on a 0-4 scale while performing several tasks involving sitting, standing, reaching, and turning, with 0 requiring the most assistance and 4 requiring no assistance while performing the task. The 25 feet walk test (25FWT) was used to evaluate the walking ability of the MS subjects (Kaufman et al., 2000). The MS subjects were required to walk 25 feet repeated in three trials at their own comfortable speed, and the time required was recorded and averaged. The Fatigue Severity Scale (FSS) was a 9-question questionnaire that allowed each subject to rate his level of fatigue between 1 (strong disagreement with the statement) and 7 (strong agreement with the statement), with a typical score of 4 and above indicating that fatigue was a significant factor of the subject's daily activities (Krupp et al., 1989). The Symbol Digit Modalities Test (SDMT) was used to evaluate the cognitive function of the MS subjects (Lewandowski, 1984). The SDMT is a simple substitution task where the subject has to use a reference key to pair specific numbers with given geometric figures within 90 seconds, and the total number of right answers is the score of cognitive abilities. The 9 hole peg test (9HPT) was used to evaluate the coordination function of the MS subjects (Goodkin et al., 1988). The subject was required

to place nine pegs into nine holes on a small platform in front of them, and then remove each peg one by one as quickly and accurately as possible. The test was repeated twice for each hand, and the time required for each iteration was recorded. All clinical tests were completed by a licensed physical therapist prior to beginning the experiment. Subject specific information is provided in Tables 4-2 and 4-3.

Table 4-1 Clinical Characteristics of MS Subjects

Subject	Age (yrs)	Years with MS	9HPT (s)	SDMT	FSS (of 7)	Berg (of 56)	25FWT (s)	Medications
S01	49	27	22.77	30	6.56	40	11.17	Ampyra, Copaxone
S02	52	15	28.65	40	6.00	46	9.32	Tysabri Baclofen,
S03	56	30	24.98	39	5.11	29	14.71	Ampyra, Interferon Beta, Amantadine
S04	48	8	17.64	50	4.50	55	6.94	Interferon Beta
S06	59	10	18.73	53	4.11	56	7.33	Tysabri
S07	50	5	21.65	48	4.44	47	6.51	Baclofen
S08	38	2	21.30	46	4.67	56	6.52	Baclofen, Ampyra
S09	57	6	27.35	37	4.78	35	18.40	
S10	50	3	20.52	44	4.67	52	7.62	

Table 4-2 Manual Muscle Test Scores of MS Subjects

Subject	Hip Abductors		Hip Flexors		Hip Extensors		Knee Flexors		Knee Extensors		Ankle Dorsiflexors		Ankle Plantarflexors	
	L	R	L	R	L	R	L	R	L	R	L	R	L	R
S01	4	4	4	4	4	4	5	4	4	4	4	4	4	4
S02	4	4	4	4	4	4	2+	5	3+	5	2	5	4	5
S03	4	3	5	5	5	3+	5	5	5	5	5	2+	5	3
S04	4	4	4+	4+	5	5	5	5	5	5	5	5	5	5
S06	5	5	5	5	5	5	5	5	5	5	5	5	5	5
S07	4	5	4	5	4	5	4	5	4	5	4	5	2	5
S08	4	4	4	4	5	5	5	5	5	5	5	5	5	5
S09	3	4	3	4	5	5	3	4	3	3	4	5	2	5
S10	4	5	4	5	5	5	5	5	5	5	5	5	5	5

Table 4-3 Modified Ashworth Scores of MS Subjects

Subject	R Knee Extensors	R Knee Flexors	R Ankle PF	R Ankle DF	L Knee Extensors	L Knee Flexors	L Ankle PF	L Ankle DF
S01	0	0	1	0	1	0	0	0
S02	0	0	0	0	0	1	1	0
S03	0	2	2	0	0	2	2	0
S04	0	1	1	0	0	1	1	0
S06	0	0	0	0	0	0	0	0
S07	0	0	0	0	0	0	0	0
S08	1	1	1	1	0	0	1	1
S09	0	2	2	0	0	2	0	0
S10	0	0	1	0	0	0	0	0

Plantarflexors (PF) and dorsiflexors (DF) abbreviated

4.2.2 Experimental Setup

Study participants were required to use their hand to track a moving target displayed and controlled by LabVIEW (National Instruments Corp., Austin, TX) on a large screen in front of them while standing (Figure 4-1). A SMARTboard (SMART Technologies, Calgary, Canada) (39 5/8" x 52 3/4") was used to display the tracking target. The position of the SMARTboard screen was adjusted such that when the subject's arm was fully extended (parallel to the ground) and pointing directly forward,

the middle of the SMARTboard screen would be centered and just out of reach of the subject's index finger. The size of the tracking trajectory was adjusted according to the length of the subject's arm from the shoulder to the tip of the index finger. Subjects stood at their comfortable stance (approximately shoulder width wide) with their toes aligned behind a fixed line marked on the force plates to ensure that they always stood at the same position. MS subjects wore a safety harness tethered to a rail system on the ceiling to prevent injury in case of falls.

Kinematics, kinetics and electromyograms (EMGs) were measured during the tasks. Subjects wore a tight-fitting sleeveless compression shirt over their own attire for better marker placement, and were set up with the full body Vicon (Vicon Motion Systems Ltd, Oxford, UK) marker set (Appendix A Table 6-2). Subjects also wore a snug fitting rubber fingertip with a smooth fabric exterior over the finger used for tracking to reduce friction on the screen. Surface EMGs were recorded bilaterally from the vastus medialis (VM), rectus femoris (RF), vastus lateralis (VL), medial hamstrings (MH), medial head of the gastrocnemius (MG), tibialis anterior (TA), and anterior deltoid (AD) from all subjects. Recording electrodes (Delsys Inc, Boston, MA) were placed on the cleansed, lightly abraded skin over each muscle belly. EMG signals were sampled at 1000 Hz and bandpass filtered (25-450 Hz) prior to sampling. Kinematic data was recorded via the six motion capture cameras at 100 Hz, and kinetic data was recorded via the two force plates at 1000 Hz. All signals were recorded in Vicon Nexus (Vicon Motion Systems Ltd).

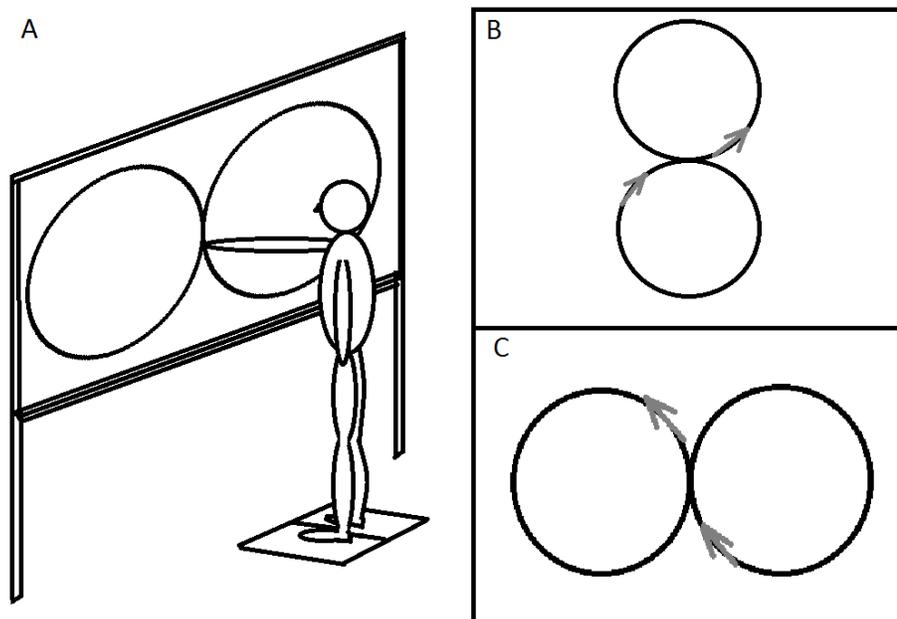


Figure 4-1 Experimental Setup. (A) Subject standing on two force plates in front of the screen used to display the tracking target. The target trajectory was displayed on the screen as either a vertical (B) or horizontal (C) figure-eight. The target would start in the middle of the figure-eight, moving in an alternate anti-clockwise and clockwise motion around the figure-eight.

4.2.3 Experimental Protocol

Subjects were presented with two different tracking trajectories—a vertical and horizontal figure-eight) (Figure 4-1 C) — and two types of tracking tasks — steady speed (SS) and ramp speed (RS) tracking. During steady speed tracking, the target would move at a constant speed of 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35 Hz, (2-12 cycles) with each trial lasting between 30-40 seconds. During ramp speed tracking, the target would start moving at 0.05 Hz, and linearly increase its speed to 0.35 Hz over a trial period of 67s. Subjects would start each trial in a standing position, with their dominant arm fully extended in front of them. They would hear four short consecutive beeps to indicate that the trial was about to start, and on the fourth beep, the target would start moving. The subjects were instructed to keep their index finger on the screen and track the target as closely and accurately as possible without changing their feet position. The tracking

trajectory was first presented as a vertical figure-eight, and the trials of the various steady speed tracking were randomized. After every three steady speed tracking trials, subjects would perform a ramp speed tracking trial. Once trials of all speeds had been completed, the tracking trajectory would be switched to the horizontal figure-eight, and the same procedure was repeated. Subjects were allowed to rest and take a seat in between trials. Subjects completed three practice steady speed tracking trials at medium speed (0.15, 0.20 and 0.25 Hz) at the beginning of the experiment for the vertical figure-eight tracking, and again when the tracking trajectory was changed to the horizontal figure-eight.

4.2.4 Data Analysis

Kinematic and kinetic data were recorded and used for the reconstruction of the subject-specific full body model in Vicon. As subjects made multiple continuous tracking cycles throughout each trial, the start and end of each cycle was marked as an event in Vicon based on the location of the finger marker on the hand that they were using to track the target. The model outputs of marker trajectory, joint angles, joint moments, center-of-mass (CoM) movement, as well as the EMG data and force plate outputs were then exported for further processing in MATLAB. All model outputs including marker trajectories, joint angular range of motion, and joint moments were low pass filtered at 10 Hz using a 4nd order zero phase Butterworth filter.

To obtain the representative average kinematic profile over one tracking cycle for each steady speed trial for each subject, each cycle was downsampled to a specific number of points depending on the speed of the trial (2000, 1000, 667, 500, 400, 333, 286 downsampled data points for speeds of 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35 Hz

respectively). These downsampled cycles were then averaged within subjects to obtain the representative average kinematic profile. The maximum and minimum amplitude values of the kinematic profile were calculated, and the peak-to-peak (PP) values were obtained from the difference of the maximum and minimum values.

Obtaining the representative kinematic profile over one tracking cycle for each ramp speed trial was not possible as the period of each cycle continuously changed as tracking speed increased throughout the trial. To obtain the maximum, minimum, and PP amplitudes of the kinematic data, the maximum and minimum values of each cycle were first determined throughout the trial. These values were then used to calculate the coefficients of a 3rd degree polynomial fit, which was used to estimate the maximum and minimum values at set time points in the ramp speed trial corresponding to each target speed. This process produced seven maximum and minimum values that characterized the kinematic data throughout the ramp speed trial. The PP values of the ramp speed kinematic data were then obtained from the difference between these corresponding maximum and minimum values.

The sagittal hip and ankle PP moments and PP angular range of motion were the primary parameters used as an indicator of the contribution of each joint during tracking. To obtain a meaningful parameter to quantify the shift in contribution between the hip and ankle, the PP moment and angular range of motion values of the hip was divided by that of the ankle to obtain a unitless ratio of hip to ankle moment and angular range of motion. This was done for each speed for both the steady speed and ramp speed trials. This step was important as it served as a method of self-normalization within each subject's joint kinematic amplitudes. For example, a high functioning subject might have

large PP joint moments at both the hip and ankle, whereas a low functioning subject might have low PP joint moments at both the hip and ankle. Also, one subject might adopt a strategy of large movements during tracking, while another might adopt a stiffening strategy to maintain balance during tracking. This creates large variability when comparing hip to hip or ankle to ankle across subjects. By taking a ratio of the PP joint kinematics, a single parameter indicative of the subject's preferred amount of hip or ankle contribution was obtained, reducing the variability during subject and group comparisons.

The center of mass (CoM) root mean square (RMS) acceleration in the anterior-posterior (A-P) and medial-lateral (M-L) directions was calculated in quiet standing and during tracking tasks to obtain a measure of balance performance. This parameter was used in previous studies to show differences in balance performance during standing in MS and Parkinson's Disease (Mancini et al., 2011; Nataraj et al., 2012a; Spain et al., 2012).

EMG signals were processed to obtain the timing and level of muscle activity during experimental procedures. All surface EMG recordings were notch filtered at 58-62 Hz to remove line noise and bandpass filtered at 30-200 Hz using 4nd order zero phase Butterworth filters (MATLAB; the Mathworks Inc., Natick, MA). For analysis, the EMG data were rectified and low pass filtered at 5 Hz using a 4nd order zero phase Butterworth filter, then ensemble averaged across cycles within each subject and trial. Analysis of the MG and TA EMGs were used to determine the amount of ankle activity present during the tracking tasks.

4.2.5 Statistical Analysis

Repeated measures ANOVA (SPSS Inc., Chicago IL) was used to compare the group difference in effect (across seven tracking speeds of 0.05 – 0.35 Hz) on the PP joint moments, PP angular range of motion, and CoM movement, between the MS and healthy control groups. For statistical analysis of clinical correlation between the joint parameters and clinical scores, a linear correlation was fit to compare parameters of maximum joint moments, angles, and PP CoM movement, to the clinical scores of the Berg balance score and the 25 foot walk test. Significance was accepted at $p < 0.05$.

4.3 RESULTS

4.3.1 Kinematic Analysis

The aim of this study was to determine if there was a difference in hip and ankle contribution, during an increasingly difficult standing arm tracking task, between individuals with MS and healthy control subjects. Kinematic profiles of hip and ankle moments and angles of both groups were examined to compare the differences in hip and ankle contribution towards functional movement during the tracking task. The focus was primarily on sagittal plane moments and angles; frontal plane moments and angles were also analyzed but showed no significant trends. Representative single subject plots from a single tracking trial are shown in Figure 4-2. Most subjects' kinematic traces exhibited a cyclic behavior characteristic of the tracking task.

Subjects showed varying amplitudes and ranges of hip and ankle moments and angles, likely related to the different postures and tracking strategies used by each subject. When each subject's representative kinematic profile per cycle was obtained and average within the group (Figures 4-3 and 4-4), both groups showed similar profiles. For the vertical tracking task (Figure 4-3), subjects typically showed a minimum hip moment (reduced hip flexion/hip extension moment) during the first 50% of the cycle, corresponding to the hip extension required to reach the upper half of the vertical figure-eight. This was followed by a maximum hip moment (increased hip flexion moment) during the last 50% of the cycle, corresponding to the hip flexion required to track the bottom half of the vertical figure-eight. This matches up with the lower hip angles (reduced hip flexion angle) in the first 50% of the cycle, followed by a peak in hip angles

(increased hip flexion angle) in the last 50% of the cycle. At the ankles, subjects typically showed a maximum ankle moment (increased ankle plantarflexion moment) during the first 50% of the cycle, corresponding to the ankle extension required to reach the upper half of the vertical figure-eight. This was followed by a minimum ankle moment (decreased plantarflexion moment) during the last 50% of the cycle, corresponding to the reduced ankle angle (increased dorsiflexion angle) required to track the bottom half of the vertical figure-eight. This profile was typically seen in both the left and right hip and ankle, as the vertical tracking task was relatively symmetrical for both legs.

The horizontal tracking task on the other hand was highly asymmetrical, requiring large medial-lateral movement and weight shifting between legs throughout the task (Figure 4-4). At the left hip, subjects typically showed a minimum hip moment (decreased hip flexion) shortly followed by a maximum hip moment (increased hip flexion moment) in the first 50% of the cycle, corresponding to the leftward movement required to track the target as it moved around the left side of the figure-eight. This matched up with the minimum hip angle (reduced hip flexion) followed shortly by a maximum hip angle (increased hip flexion) in the first 50% of the cycle. This profile was similar at the right hip, but occurred in the last 50% of the cycle, where the subject was tracking the right side of the figure-eight. At the left ankle, subjects typically showed a maximum ankle moment (increased ankle plantarflexion moment), followed by a minimum ankle moment (decreased plantarflexion moment) in the last 50% of the cycle. This corresponded to the increased ankle plantarflexion moment resulting from the weight shift to the left, required to reach the left half of the horizontal figure-eight. The left ankle angle showed a large minimum angle that went into ankle plantarflexion

(negative angle) in the last 50% of the cycle, matching up with the plantarflexion movement at the left ankle required to reach the right side of the horizontal figure-eight. This profile was similar for the right hip, with an approximate 50% phase difference due to the asymmetry of the tracking task.

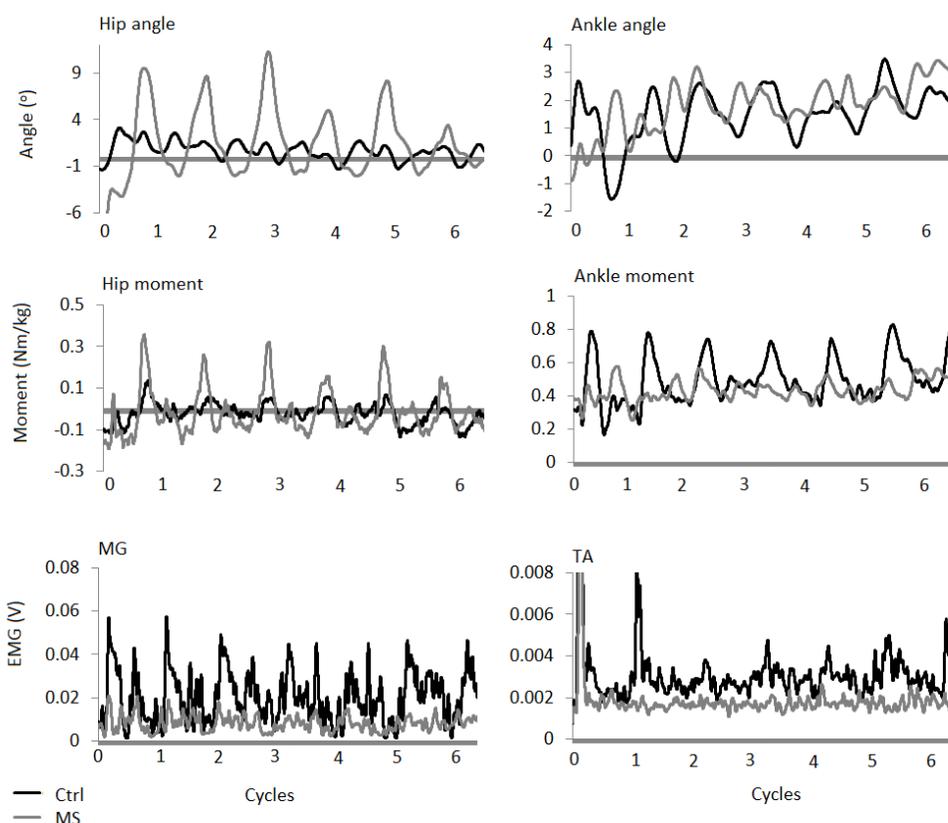
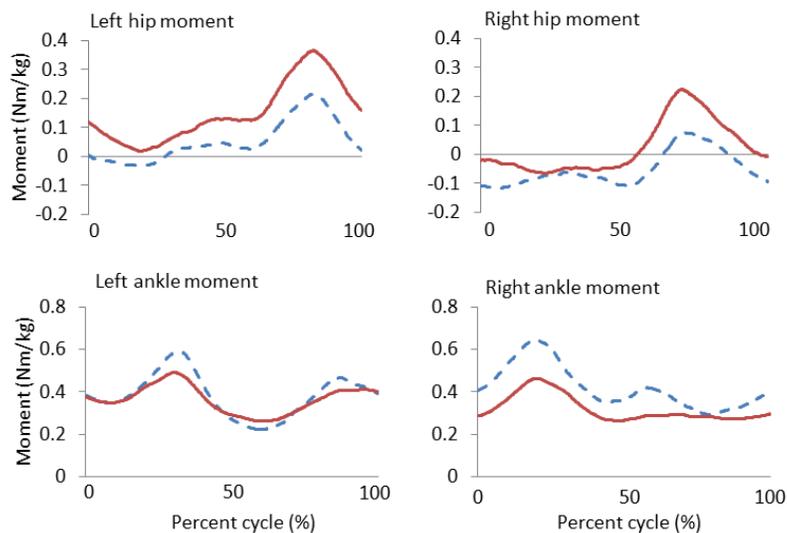


Figure 4-2 Representative Single Subject Data. Representative kinematic, kinetic and EMG data from a representative control and a representative MS subject during a vertical 0.25 Hz tracking trial. At the hip, flexion angles and external moments are positive, extension angles and external moments are negative. At the ankle, dorsiflexion angles and external moments are positive, plantarflexion angles and external moments are negative.

The group averages of EMG (Figure 4-5) showed larger amplitudes of activation at the TA and MG muscles for the control group, compared to the MS group. EMG activation followed a typical double peak profile in each half of the cycle, likely related

to the movement and weight shifting pattern inherent to the tracking task. This increase in EMG amplitude in the control group is consistent with the larger maximum moments observed in the ankle joint moment plots for the same speeds (Figures 4-3 and 4-4).

Vertical tracking moment



Vertical tracking angle

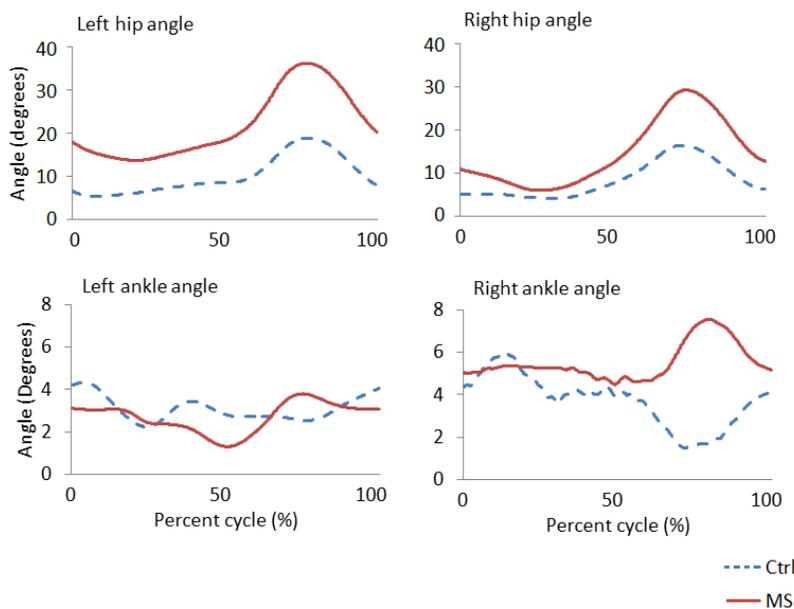


Figure 4-3 Group Average Kinematic and Kinetic Plots for Vertical Figure-Eight Tracking. MS (solid line) and control (dashed line) group averages of hip and ankle sagittal plane moments and sagittal plane angles during a 0.20 Hz vertical SS tracking task. Each plot represents a full cycle of tracking (0-100% cycle) around the figure-eight trajectory. Positive moments indicate hip extension or ankle plantarflexion moments, and negative moments indicate hip flexion or ankle dorsiflexion moments. Positive angles indicate hip flexion or ankle dorsiflexion, and negative angles indicate hip extension or ankle plantarflexion. The MS group was observed to have increased hip moment and angular range of motion and reduced ankle moment and angular range of motion compared to the control group.

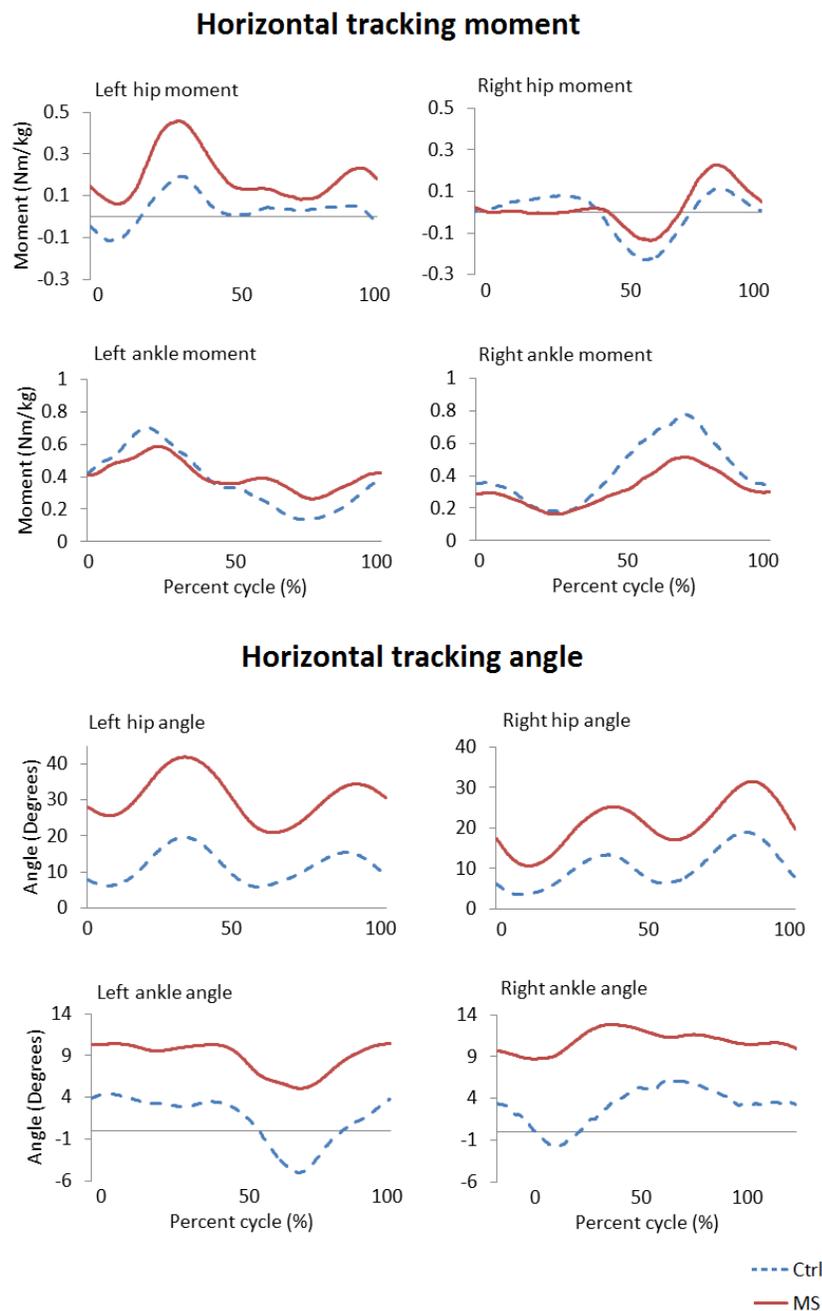


Figure 4-4 Group Average Kinematic and Kinetic Plots for Horizontal Figure-Eight Tracking. MS (solid line) and control (dashed line) group averages of hip and ankle sagittal plane moments and sagittal plane angles during a 0.20 Hz horizontal tracking task. Each plot represents a full cycle of tracking (0-100% cycle) around the figure-eight trajectory. Positive moments indicate hip extension or ankle plantarflexion moments, and negative moments indicate hip flexion or ankle dorsiflexion moments. Positive angles indicate hip flexion or ankle dorsiflexion, and negative angles indicate hip extension or ankle plantarflexion. The MS group was observed to have increased hip moment and angular range of motion and reduced ankle moment and angular range of motion compared to the control group.

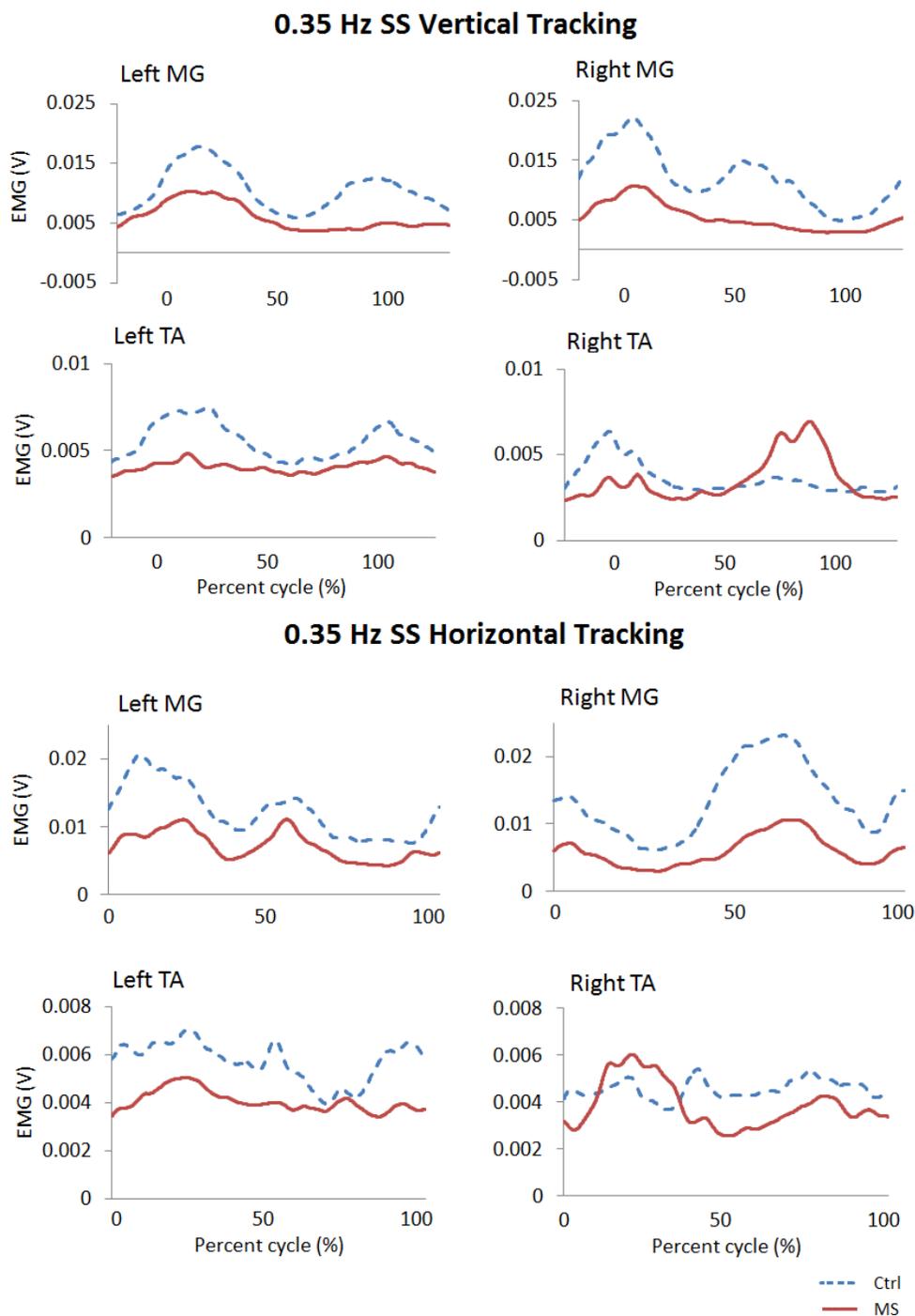


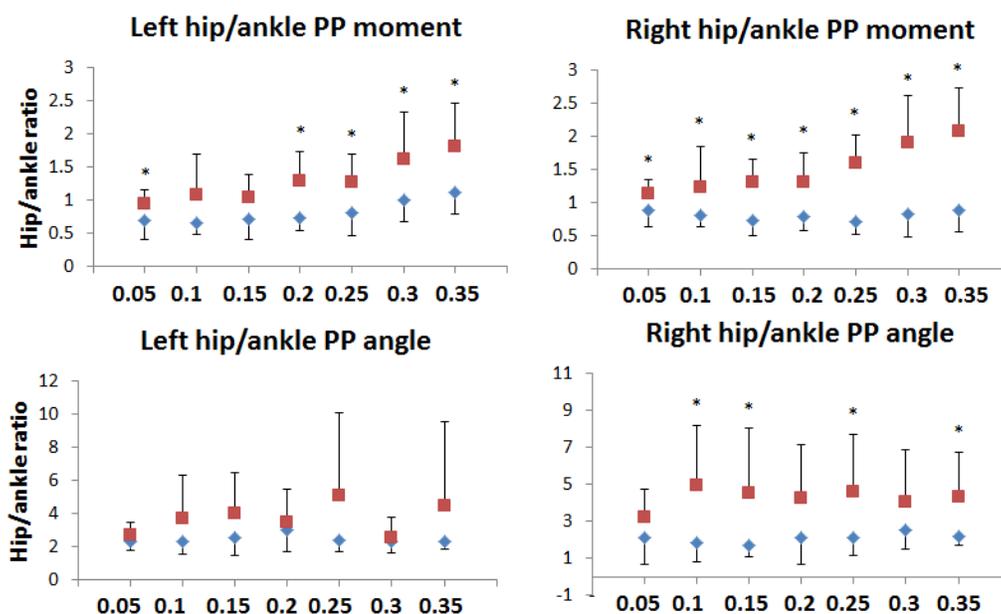
Figure 4-5 Group Average EMG Plots. MS (solid line) and control (dashed line) group averages of the left and right leg MG and TA muscles during a 0.35 Hz vertical and horizontal SS tracking task. Each plot represents a full cycle of tracking (0-100% cycle) around the figure-eight trajectory. The MS group was observed to have reduced MG and TA activity compared to the control group.

4.3.2 Hip/ankle PP Joint Moments and Angles

In general, there was a larger relative contribution from the hip, compared to the ankle, for standing, figure-eight tracking movements in MS subjects. Inspection of the group averaged kinematic and kinetic profiles for a single speed (Figures 4-3 and 4-4) suggested that the MS group had greater PP moments and angles at the hips, and generally smaller PP moments and angles at the ankles. The ratio of PP hip moments and angles relative to the PP ankle moments and angles were calculated for each group, for each test speed and are shown in Figure 4-6. The magnitudes of the PP hip/ankle group averaged parameters were larger in the MS group, across all tracking speeds, and for both the vertical and horizontal steady speed tracking (Figure 4-6). The difference in PP hip/ankle joint parameters was significant between groups for all tracking paradigms (Repeated Measures ANOVA $p < 0.05$), and for 10 out of 16 parameters (Table 4-4).

The hip/ankle parameters from the ramp speed tracking showed a similar trend as the SS task, with the MS group showing larger hip/ankle PP joint moments and angles during both vertical and horizontal ramp speed tracking, compared to the control group (Figure 4-7). Both groups were significantly different during vertical and horizontal tracking (repeated measures ANOVA $p < 0.05$), but significance was only detected at the right hip/ankle PP moment during vertical ramp speed tracking, and the left and right hip/ankle PP moments during horizontal ramp speed tracking (Table 4-4). There was also an increase in hip/ankle ratio with increasing tracking speed in both the MS and control group, which was particularly noticeable in the left and right hip/ankle PP moment during both vertical and horizontal ramp speed tracking.

Vertical SS tracking



Horizontal SS tracking

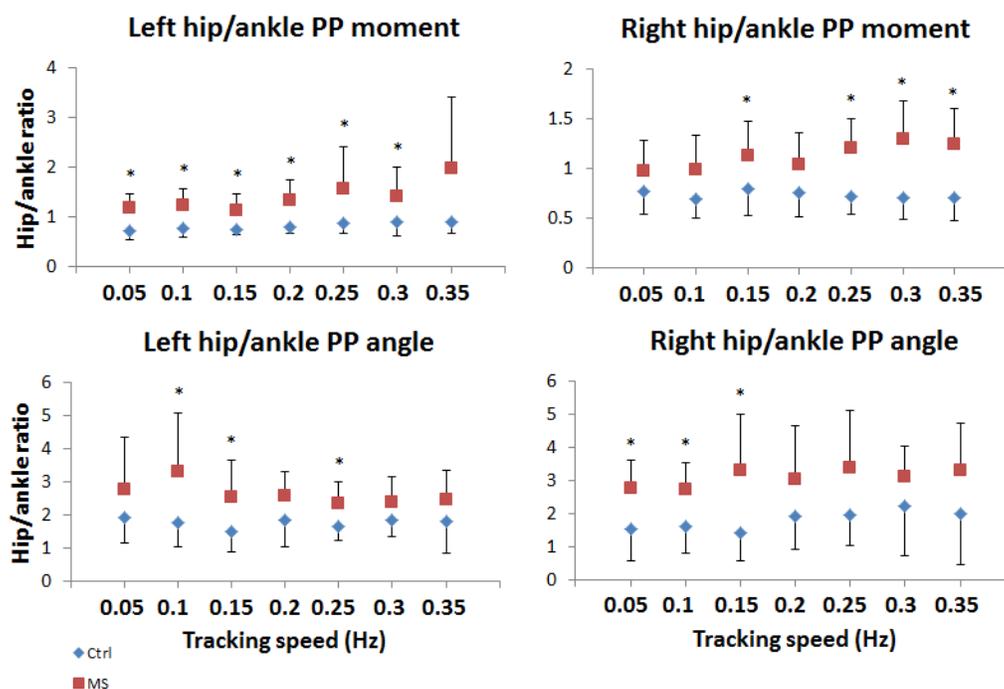


Figure 4-6 PP Hip/Ankle Ratio of Joint Kinematics and Kinetics for each Speed. Group averages of PP hip/ankle ratio of joint moments and joint angles for each steady speed (SS) for vertical and horizontal tracking. The MS group showed an increased PP hip/ankle ratio for joint moments and angles across all tracking speeds, compared to the control group. * Indicates significance across pairwise comparisons between same speeds ($p < 0.05$). Standard deviation bars are indicated for each speed (Negative bars for control group and positive bars for MS group).

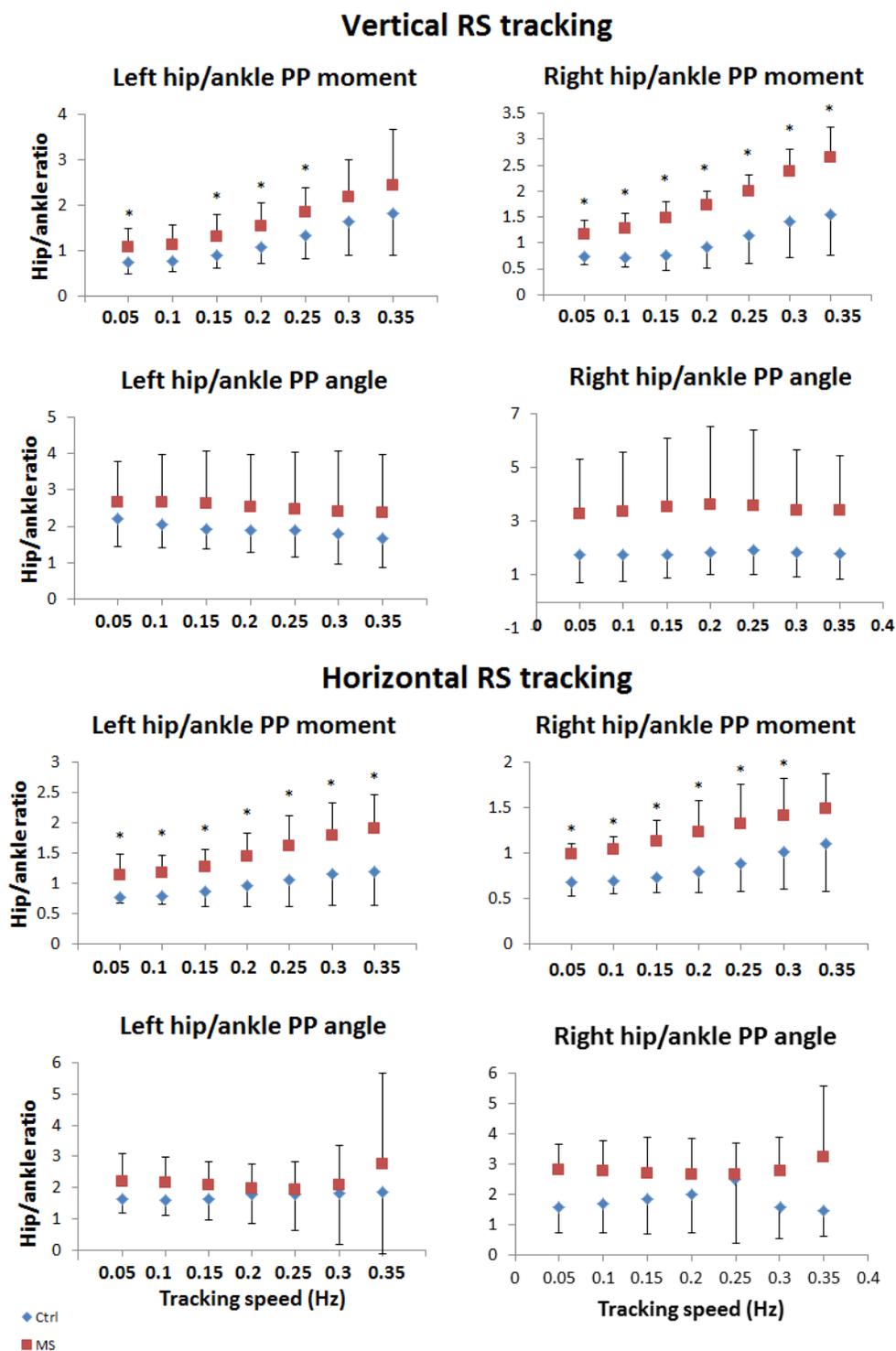


Figure 4-7 PP Hip/Ankle Ratio of Joint Kinematics and Kinetics for each Speed. Group averages of PP hip/ankle ratio of joint moments and joint angles for increasing tracking speed for vertical and horizontal ramp speed (RS) tracking are shown. The MS group showed an increased PP hip/ankle ratio for joint moments and angles across all speeds throughout the RS trials, compared to the control group. * Indicates significance across pairwise comparisons between same speeds ($p < 0.05$). Standard deviation bars are indicated for each speed (negative bars for control group and positive bars for MS group).

Table 4-4 Significance of PP Hip/ankle Parameters

	Significance			
	Vertical SS	Horizontal SS	Vertical RS	Horizontal RS
Group	0.006*	0.000*	0.009*	0.013*
Left hip/ankle PP moment	0.011*	0.003*	0.088	0.007*
Right hip/ankle PP moment	0.000*	0.004*	0.000*	0.004*
Left hip/ankle PP angle	0.106	0.016*	0.252	0.346
Right hip/ankle PP angle	0.030*	0.029*	0.077	0.063

p-values for vertical and horizontal steady speed (SS) and ramp speed (RS) tracking tested with repeated measures ANOVA. Group analysis compares all four parameters between the MS and control group. Significance ($p < 0.05$) is marked with a *.

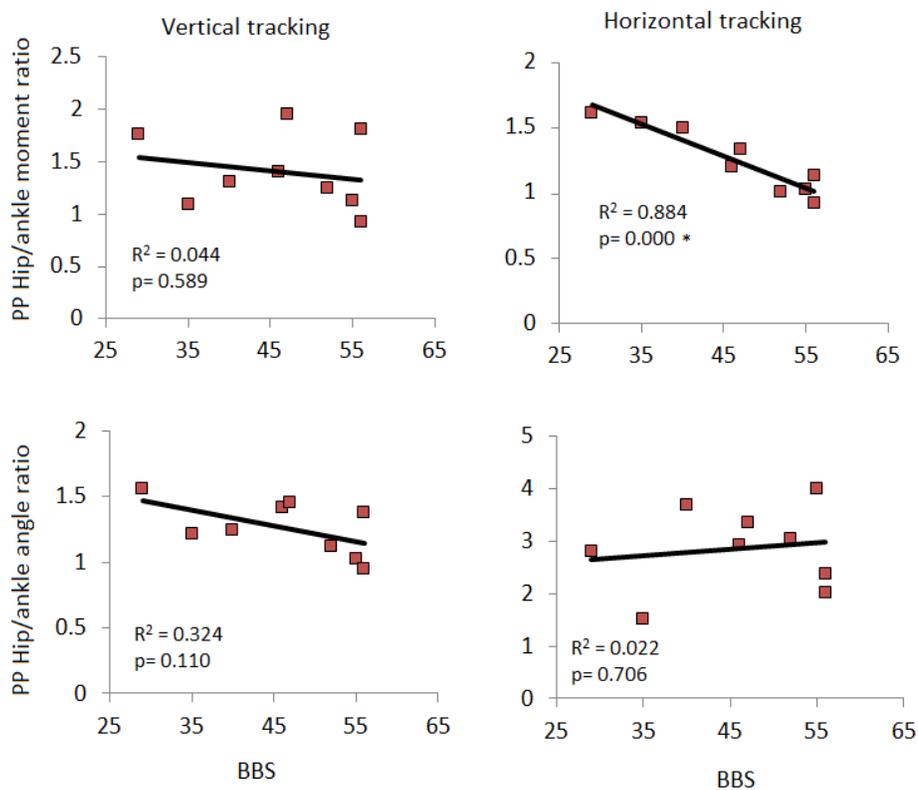


Figure 4-8 Steady Speed PP Hip/ankle Ratios Averaged Across All Speeds compared to BBS. The MS subjects showed a strong regression between PP hip/ankle moment ratio and BBS during steady speed horizontal tracking, demonstrating that the PP hip/ankle moment ratio increased with decreasing BBS. * indicates regression significance ($p < 0.05$).

The PP hip/ankle ratio was related to functional balance. For the MS group, the PP hip/ankle parameters for each subject were averaged together across all seven tracking speeds, then averaged between the left and right leg of each subject for regression with the BBS (Figure 4-8). The MS group showed a significant correlation between the PP hip/ankle moment ratio and BBS during the horizontal steady speed tracking task ($R^2 = 0.884$, $p = 0.000$), demonstrating increasing PP hip/ankle moment ratio with increasing impairment (decreasing BBS).

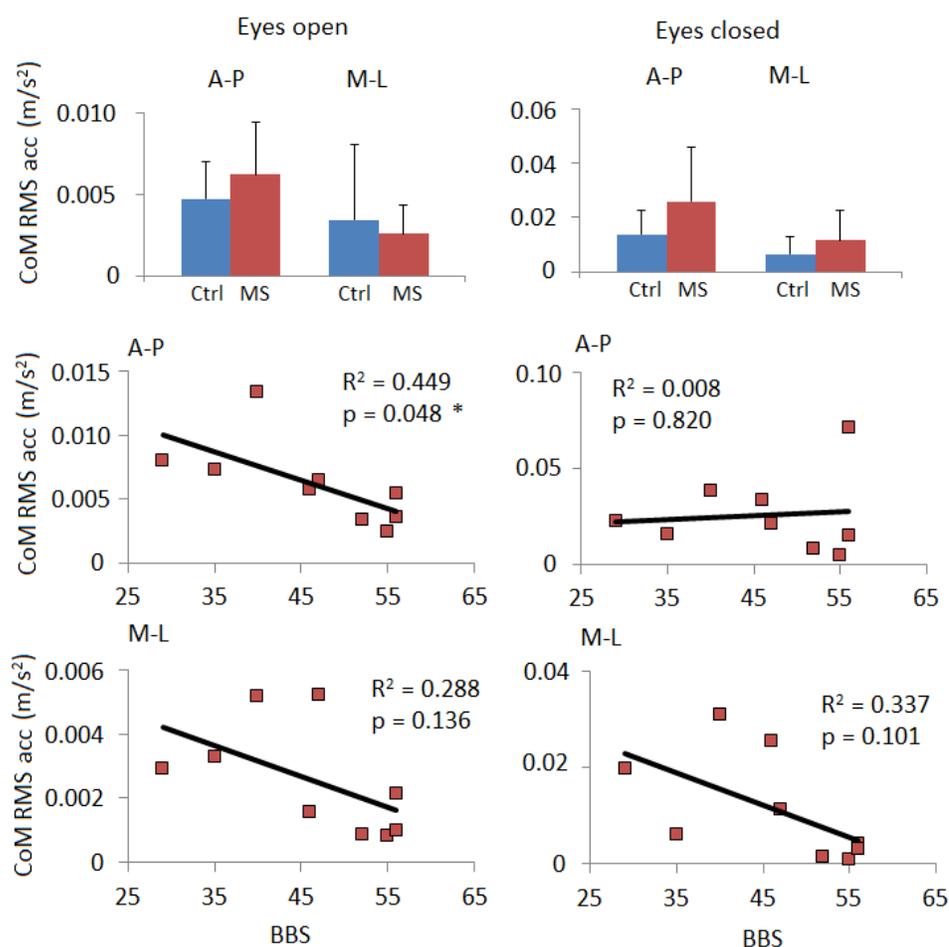


Figure 4-9 Quiet Standing Balance Measures. No significant group differences in CoM RMS acceleration during quiet standing in both eyes open and eyes closed conditions was observed (repeated measures ANOVA $p > 0.05$). The MS group demonstrated a good regression between CoM RMS acceleration in the anterior-posterior direction to BBS in the eyes open condition. Positive standard deviation bars are indicated for group data. * indicates significant regression ($p < 0.05$).

During quiet standing, the CoM RMS acceleration (A-P) in the MS and control group increased in the eyes closed condition (Figure 4-9). The MS group demonstrated higher CoM RMS acceleration (A-P) than the control group during all conditions. However, this difference was not significant (ANOVA, $p < 0.05$). The MS group demonstrated increasing CoM RMS acceleration in the anterior-posterior and medial-lateral directions with increasing impairment (decreasing BBS) during the eyes open condition, showing a strong regression between CoM RMS acceleration (A-P) and BBS ($R^2 = 0.449$, $p = 0.048$).

During steady speed tracking, the CoM RMS acceleration increased with increasing tracking speed for the MS and control group (Figure 4-10). However, the CoM RMS acceleration (A-P) was not significantly different between groups (repeated measures ANOVA $p < 0.05$) and across the same speeds (pairwise comparison ANOVA $p < 0.05$).

In the MS group, the CoM RMS acceleration (A-P) was averaged across tracking speeds for each subject and compared to the corresponding BBS (Figure 4-11). The MS subjects showed decreasing CoM RMS acceleration with increasing impairment (decreasing BBS) but no significant regressions were observed.

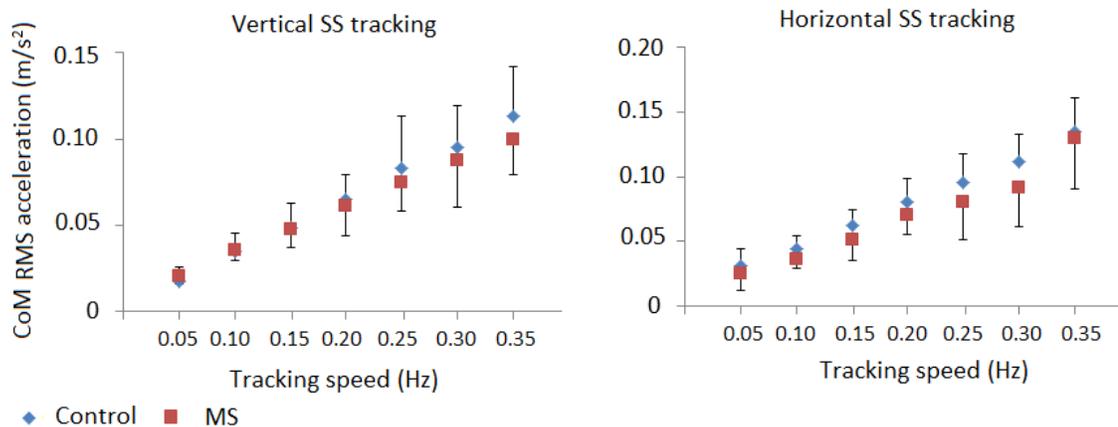


Figure 4-10 CoM RMS Acceleration (A-P) Across Steady Speed Tracking. Both groups showed increasing CoM RMS acceleration with increasing tracking speed. No group differences were observed (repeated measures ANOVA, vertical tracking $p=0.513$, horizontal tracking $p=0.159$). Standard deviation bars are indicated for each speed (positive bars for control group and negative bars for MS group).

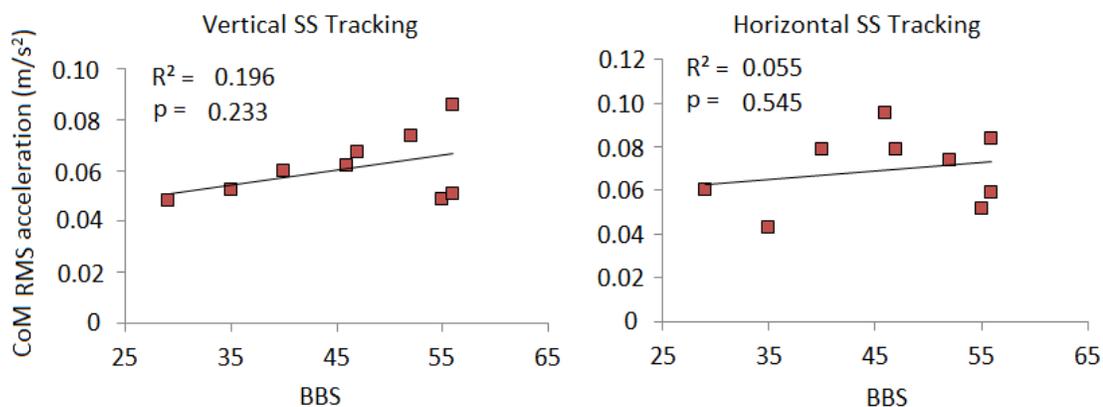


Figure 4-11 Regression Between CoM RMS Acceleration (A-P) Averaged Across All Speeds to BBS. No significant regressions were seen between the CoM RMS acceleration and BBS during the vertical and horizontal tracking in MS ($p>0.05$).

4.4 DISCUSSION

Results from this study showed a greater contribution from the hip than the ankle during a standing arm tracking task in people with MS, compared to healthy controls. Although both groups showed increasing ratios of hip/ankle joint moments with increasing tracking speeds, the amount of sagittal hip to ankle contribution was higher in the MS group than the control group for vertical and horizontal tracking, during both steady speed and ramp speed tracking. During the tracking tasks, balance performance (measured by CoM RMS acceleration) was not significantly different between groups, or correlated to clinical measures of balance in MS. These results indicate a shift to an increased hip strategy during arm tracking involving whole body movement in people with MS, while maintaining comparable balance performance to healthy control subjects.

4.4.1. Shift in Movement Strategy with Increasing Perturbation

There is a shift towards a hip strategy during increasing challenges to balance. During tracking, both MS and control groups utilized an increased hip strategy with increasing perturbation size, reflected by an increasing PP hip/ankle moments of both groups with increasing tracking speed. The overall increase in moments at the hip and ankle was consistent with an increase in difficulty of the tracking task, where the subject was required to move faster to keep track of the target. It is likely that the subjects utilized combined hip and ankle strategies for adaptable control of CoM in the sagittal plane (Nashner and McCollum, 1985) in different magnitudes and temporal relations (Horak and Nashner, 1986) to optimally maintain balance during tracking. The ankle strategy dominated during low speed tracking as the ankle strategy repositioned the CoM

by moving the entire body as a single segmented inverted pendulum (Kuo and Zajac, 1993) through the production of ankle torque, suitable for correcting small amounts of sway resulting from slow, small perturbations and maintaining vertical posture while moving the CoM (Kuo, 1995). As the tracking speed increased, there was a need for an increased hip strategy, which moved the body as a double segment inverted pendulum (Runge et al., 1999), with counter phase motions at the ankles and hip, suitable for quick postural adjustments for correction of larger, more rapid perturbations. This shift towards a hip strategy during increasing external perturbations has been observed in healthy individuals (Liaw et al., 2009), and it is likely that both groups utilized this strategy when the tracking speed increased.

There was a larger shift towards a hip strategy in MS than healthy control subjects. Although the shift towards a hip strategy with increasing tracking speed was observed in both groups, the MS subjects generally used the hip strategy more than the control subjects overall. This was reflected by the consistently larger PP hip/ankle moments and angles in the MS group compared to the control group for all tracking speeds. This shift towards a hip strategy in the MS group is consistent with studies that report increased hip contributions during external perturbations in neurologically impaired populations (Termoz et al., 2008; Hwang et al., 2009). The ankle strategy typically dominates during normal stance and comfortable balance tasks, whereas a narrow stance width or increased balance difficulty requires changes to the whole body movement pattern (Danis et al., 1998) and decreases the role of the ankle while increasing the role of the hip (Gatev et al., 1999). This shift in contribution away from the ankle might be explained by limits of ankle muscles, which are largely responsible for

phasic control of anterior-posterior balance during quiet standing (Borg et al., 2007). However, the ankle strategy requires more muscle activation than the hip strategy with increased perturbation size, and a combination of ankle and hip movement with an increased ratio towards the hip, is favored with increasing speed (Kuo and Zajac, 1993). Hence, deficits at the ankle in people with MS might be responsible for the baseline shift towards the hip strategy during challenging perturbations.

4.4.2 Interaction Between Movement Strategy and Balance

Although the MS group demonstrated reduced balance measured clinically with the BBS and kinematically during quiet standing, the balance performance during tracking was not significantly different between the MS and control group, and not correlated to BBS in MS. This was measured using the CoM RMS acceleration, which has been identified as a possible primary sensory input for maintaining balance (Nataraj et al., 2012a, 2012b). This indicates that the MS group was able to sufficiently maintain comparable balance performance to the control group during tracking. Studies have shown that ataxic-spastic MS subjects are able to compensate for deficits like proprioceptive loss, with more efficient control strategies during standing to achieve the same postural performance as only spastic MS subjects (Rougier et al., 2007). Furthermore, minimally impaired adults with MS were also able to use an adapted reaching strategy that allowed them to stay within their reduced limits of stability to perform the same reaching task as healthy control subjects (Karst et al., 2005). Hence, it is possible that the MS subjects in this study were able to compensate for balance deficits and maintain balance performance during tracking.

The relationship between the amount of hip strategy used and balance impairment in MS is unclear. Although the PP hip/ankle moment ratio was strongly correlated to BBS during horizontal tracking, no clear regression was observed during vertical tracking. It is possible that the larger size of the horizontal tracking task required a greater range of whole body movement, resulting in balance deficits driving the use of the hip strategy in MS. However, without a similar trend seen during vertical tracking, there is insufficient evidence to implicate balance impairment as a driving force for a shift towards the hip strategy in MS.

4.4.3 Causes of Changes to Movement Strategy

Deficits in sensory inputs and/or errors in motor commands in people with MS might contribute to an increased hip strategy. In MS, proprioceptive sensory feedback signals might be erroneous or delayed, causing a decreased use of proprioceptive information (Feys et al., 2006). Additionally, prolongation of spinal cord somatosensory conduction can cause delays in postural response onset (Cameron et al., 2008), indicating that people with MS receive delayed somatosensory information, and subsequently respond slower to perturbations. As multiple, redundant local sensory signals are integrated as part of a hierarchical feedback control system (Ting, 2007), a decrease in one aspect of sensory input might increase reliance on other sensory signals. Additionally, damage to descending motor pathways might result in inaccurate motor commands that are compensated later through additional sensory-based corrections (Casadio et al., 2008) and subtle alterations in sensorimotor control (Solaro et al., 2007). As functional performance might be correlated to the number of reliable sensory inputs (Cattaneo and Jonsdottir, 2009), sensory deficits in MS are likely to cause a change in

strategy. Studies of postural strategies used by patients with sensory loss have shown that both biomechanical constraints and sensory information available are important to strategy selection. For example, patients with complete vestibular loss are unable to utilize a hip strategy for efficient control of equilibrium and balance recovery (Horak et al., 1990). However, impaired somatosensory information from the lower limbs results in an inability to use an ankle strategy effectively, and increased reliance on a hip or stepping strategy (Horak et al., 1990; Runge et al., 1994) Hence, it is likely that the MS subjects in this study utilized an increased hip strategy due to sensorimotor impairments.

The ability to correctly anticipate a postural change or perturbation might be impaired in MS, resulting in less automated and insufficient postural control during very challenging perturbations, similarly seen in elderly (Laessoe and Voigt, 2008). In this study, we used an internal perturbation in the form of a continuous tracking task, presenting a certain amount of predictability in the target. As this was a standing arm tracking task, the continuous arm movement likely involved anticipatory non-focal muscle activity that transported the arm and resisted the perturbation caused by the arm movement to minimize the impact of predictable perturbations (Tyler and Karst, 2004). This movement also required dynamic changes in the trunk and lower extremities to stabilize the body and initiate and assist whole body reaching (Kaminski and Simpkins, 2001). The MS subjects might have a diminished ability to produce directional specific patterns of anticipatory muscle activation and postural shifts during a rapid arm movement, resulting in reduced balance function (Krishnan et al., 2012) and requiring an increased hip strategy. The inability to anticipate postural perturbations might be related to weakness of muscles associated with balance recovery (Carty et al., 2012), as well as

asymmetries in lower limb power (Chung et al., 2008). Hence, the inability to make predictive postural changes might diminish baseline balance performance in MS, prompting the use of an increased hip strategy.

4.4.4 Clinical Implications for Rehabilitation

Measurements of hip compensatory strategies might provide estimates of impairment that are not obtainable from functional measures. Currently, the Expanded Disability Status Scale (EDSS) and Multiple Sclerosis Functional Composite (MSFC) are used for assessing MS impairment, particularly for clinical trials. These scales are multidimensional and place emphasis on ambulation and balance function. Several clinical measures of balance like the Berg Balance Scale, Timed 25-Foot Walk, Six-minute Walk, and Timed Up and Go, have been used to reliably quantify the level of balance impairment in moderately impaired subjects, but might not be as useful in a heterogeneous or more impaired clinical population (Learmonth et al., 2012).

Additionally, the functional reach test, which has been used to distinguish between MS individuals with poor balance (Frzovic et al., 2000), might be a weak measure of stability limits as it does not take into account compensatory mechanisms (Jonsson et al., 2003).

As the compensatory hip strategies employed by people with MS might vary with impairment, clinical assessments of walking and balance become less accurate in assessing the underlying degree of functional impairment. The protocol in the current study distinguished the difference in hip versus ankle strategy between individuals with MS and healthy control subjects in the context of a voluntary movement, indicating potential as a measure of pathophysiology in MS.

An improved understanding of the interactions between hip versus ankle strategy and balance function might help to direct rehabilitation interventions in MS. There is currently no widely used standard of prescribed rehabilitation that improves balance in people with MS. Often, AFOs or walking aids are prescribed to assist with walking and balance, and to prevent falls and accidents during ambulation. With the reduction in balance function often occurring in the early stages of MS, it is likely that balance rehabilitation in different sensory contexts has been shown to be useful in reducing the rate of falls and improving dynamic balance in people with MS (Cattaneo et al., 2007). For example, asymmetrical light weight placement on the torso has been shown to assist MS patients in maintaining balance during static and dynamic activities (Gibson-Horn, 2008; Widener et al., 2009). Training interventions focusing on mechanisms related to dynamic stability have also been shown to increase ankle strategy (Lindemann et al., 2012), plantarflexor muscle strength, rate of hip moment generation, and neuromuscular coordination, improving the ability to regain balance during forward falls in elderly (Aragão et al., 2011; Arampatzis et al., 2011). Hence, by understanding how compensatory strategies affect performance during functional movements, unique rehabilitation interventions can be used to either strengthen the underlying joint weakness, or bolster the effectiveness of the compensatory strategy.

In conclusion, the observation that PP hip/ankle ratio for joint moments was significantly larger in the MS group than control group suggests that people with MS increase their hip contribution and reduce their ankle contribution during standing arm tracking compared to age-matched controls. This adapted strategy is likely due to

increased sensorimotor impairment at the ankle, but it allows people with MS to achieve a similar task performance as controls.

CHAPTER 5 *Integration of Results*

5.1 INTRODUCTION

5.1.1 Brief Summary

The work presented in this dissertation investigated the effect of sensorimotor impairments at the hip and ankle on the function and strategy during walking and reaching while standing in people with multiple sclerosis (MS). In Chapter 2, we found that coordination was more impaired at the ankle than the hip during imposed bilateral leg movement in MS, resulting in hip performance being a strong predictor of clinical function. Increased impairment at the ankle was also observed during overground gait in Chapter 3, where the MS group demonstrated a reduced ankle contribution during the stance phase in conjunction with poor modulation of gastrocnemius activity. In Chapter 4, the MS group demonstrated an increased hip versus ankle joint contribution during various challenging standing reaching tasks, while maintaining comparable balance performance compared to the healthy controls. Taken together, these findings indicate an increased impairment and reduced reliance on the ankle compared to the hip, resulting in a high dependence on the functional capacity of the hip to maintain walking and balance function.

5.1.2 Is the Shift Towards a Hip Strategy a Viable Solution for Functional Performance?

In MS, impaired central activation relating to ankle weakness (Ng et al., 2004; Reich et al., 2008) can result in ankle torque asymmetries (Kalron et al., 2011b) and foot drop (DeLisa et al., 1985), reducing the functional capacity of the ankle during gait and balance. During walking, this reduction in ankle function likely forces a compensatory strategy involving increased hip abduction for toe clearance commonly seen in stroke (Kuan et al., 1999; Kerrigan et al., 2000), and increased hip flexion for additional propulsion during gait (Jonkers et al., 2009). From a biomechanical standpoint, leveraging the additional degree of freedom (hip abduction) and muscular capacities of the hip and knee to account for the deficit in ankle range and power is a sound strategy in overcoming the ankle deficits. During balance, the impaired ankle might not be able to make reliable corrections during perturbations, causing an increased reliance on the hip to maintain balance, similar to that seen during standing arm tracking in Chapter 4. The shift from an ankle to hip strategy in MS might involve stiffening of the ankles while using hip movement to change the CoM and resist perturbations, thereby utilizing the lesser impaired joint and simplifying balance control by reducing the number of joints involved. Although the use of an increased hip strategy might help to maintain gait and balance performance, it might encourage an increasing disuse of the ankle and a drift towards an increasing hip strategy over time with disease progression. This might result in eventual saturation of hip effort and neglect of ankle's function, limiting the peak functional capacity in MS.

5.1.3 Considerations for Rehabilitation

The results from this dissertation suggest that novel strategies for addressing impairment in the form of joint-specific rehabilitation methods aimed at improving

walking and balance function might be developed for MS. Current solutions that address ankle weakness in patients with MS include the use of an ankle foot orthosis (AFO) that limits the degrees of freedom at the ankle (Cattaneo et al., 2002a), and a functional electrical stimulator (FES) that provides peroneal nerve stimulation (Upshaw and Sinkjaer, 1997) for prevention of foot drop. However, the merits and long term effects of using an AFO or FES are unclear. Static (complete restriction of range of motion) and dynamic (partial restriction of range of motion) AFOs have been shown to improve static balance, while dynamic balance was more impaired by static AFOs than dynamic AFOs (Cattaneo et al., 2002a). The decrease in energy cost when walking with a spring-like energy-storing AFO in central neurological patients was not induced by an augmented net ankle push-off, but by the AFO partially taking over ankle work (Bregman et al., 2012). In MS subjects with dorsiflexion and eversion weakness, no statistically significant improvement was found performing timed tasks of functional ambulation with an AFO (Sheffler et al., 2008). This is evidence that an AFO might not be the optimal solution to addressing ankle dysfunction. Similarly, the effects of using an FES have produced mixed results. The use of an FES in MS has been shown to reduce the physiological cost of gait (Paul et al., 2008), improve gait function with and without the FES (Stein et al., 2010), and increase the motor evoked potential and strength at the ankle following long term use (Everaert et al., 2010). However, the use of an FES has also been shown to improve the quality of life in MS, but is not correlated to objective measures of gait (Barrett and Taylor, 2010).

Rehabilitation interventions can be joint specific, depending on the level of joint impairment of the individual with MS. Instead of addressing ankle weakness with a

device that limits ankle range of motion or supplements ankle power generation, a rehabilitation regime that strengthens the ankle might be beneficial to maintaining range of motion and encouraging ankle muscle activity in mild to moderately impaired MS patients. For example, endurance exercises focused on the dorsiflexors have been shown to improve walking function in MS patients with foot drop (Mount and Dacko, 2006). Conversely, in MS patients with highly impaired ankle joints unresponsive to rehabilitation, improving the functional capacity of the lesser impaired hip joint through endurance or coordination exercises might improve the effectiveness of the inherent hip strategy in MS. Resistance training has been shown to improve muscle strength, functional capacity (Dalgas et al., 2009; Cakt et al., 2010; Eftekhari et al., 2012), and gait kinematics (Gutierrez et al., 2005) without adverse effects (Sabapathy et al., 2011). Similarly, endurance exercises (Dettmers et al., 2009) have resulted in increased walking distance in MS. In more impaired individuals, bodyweight-supported robot-assisted training can also be used to improve gait performance (Beer et al., 2008; Wier et al., 2011). Clearly, the appropriate strength and endurance rehabilitative intervention can result in increased function in MS.

5.2 FUTURE STUDIES

Further investigation into the impairments measured in Chapter 2 might provide information that could formulate a novel rehabilitation intervention. In Chapter 2, reduced coordination function in MS was quantified as an increased negative work ratio despite no observable differences in peak torque amplitude or phasing. It is possible that providing additional sensory input might serve as a feedback mechanism to correct for the coordination errors during imposed bilateral leg movement. For example, visual feedback overlaying the joint angular movement with the joint torque produced might provide important information regarding the appropriate timing of joint flexion and extension. This visual feedback could also be used to monitor the torque or effort level of each subject. For example, keeping the leg robot in a stationary setting, the subject could be required to produce a variety of unilateral or bilateral isometric contractions by following the predefined torque trace on the screen. These predefined torque traces could follow a square wave, a triangular wave, a sinusoidal wave, or a ramp and hold. This protocol could be useful in further determining the effect of discoordination on torque production. It could also be used as part of an intervention study to investigate the effect of torque coordination training in MS.

In Chapter 4, the hip versus ankle contribution during standing arm tracking movement was higher in the MS group than the control group, but no definitive correlation to clinical measures of balance could be determined. This could be attributed to the nature of the balance perturbation task, which required large arm movements in the frontal plane, but might not necessarily have challenged the limits of stability sufficiently in the anterior-posterior direction. In future studies, an anterior-posterior tracking target

could be presented on a screen lying horizontally in front of the subject at waist-height, thereby challenging the subject's dynamic balance ability in the anterior-posterior direction.

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APPENDIX A

Table A-1 Vicon Lower Body Marker Locations

Hip	LASI	Left anterior superior iliac spine
	RASI	Right anterior superior iliac spine
	SACR	Sacrum
Left leg	LTHI	Mid-point of left thigh
	LKNE	Left lateral knee
	LTIB	Mid-point of left shank
	LANK	Left malleolus
	LHEE	Left heel
	LTOE	Base of left foot 2nd toe
Right leg	RTHI	Mid-point of right thigh
	RKNE	Right lateral knee
	RTIB	Mid-point of right shank
	RANK	Right malleolus
	RHEE	Right heel
	RTOE	Base of right foot 2nd toe

Table A-2 Vicon Full Body Marker Locations

Body segment	Marker name abbreviated	Position
Head	LFHD	Left forehead
	RFHD	Right forehead
	LBHD	Left head rear
	RBHD	Right head rear
Torso	C7	Spine C7
	T10	Spine T10
	CLAV	Middle of both clavicles
	STRN	Bottom of sternum
	RBAK	Right scapula
	Left arm	LSHO
LELB		Left lateral elbow
LWRA		Left wrist medial epicondyle (radius)
LWRB		Left wrist lateral epicondyle (ulna)
LFIN		Base of left index finger
Right arm	RSHO	Right shoulder acromion
	RELB	Right lateral elbow
	RWRA	Right wrist medial epicondyle (radius)
	RWRB	Right wrist lateral epicondyle (ulna)
	RFIN	Base of right index finger
Hip	LASI	Left anterior superior iliac spine
	RASI	Right anterior superior iliac spine
	SACR	Sacrum
Left leg	LTHI	Mid-point of left thigh
	LKNE	Left lateral knee
	LTIB	Mid-point of left shank
	LANK	Left malleolus
	LHEE	Left heel
	LTOE	Base of left foot 2nd toe
Right leg	RTHI	Mid-point of right thigh
	RKNE	Right lateral knee
	RTIB	Mid-point of right shank
	RANK	Right malleolus
	RHEE	Right heel
	RTOE	Base of right foot 2nd toe

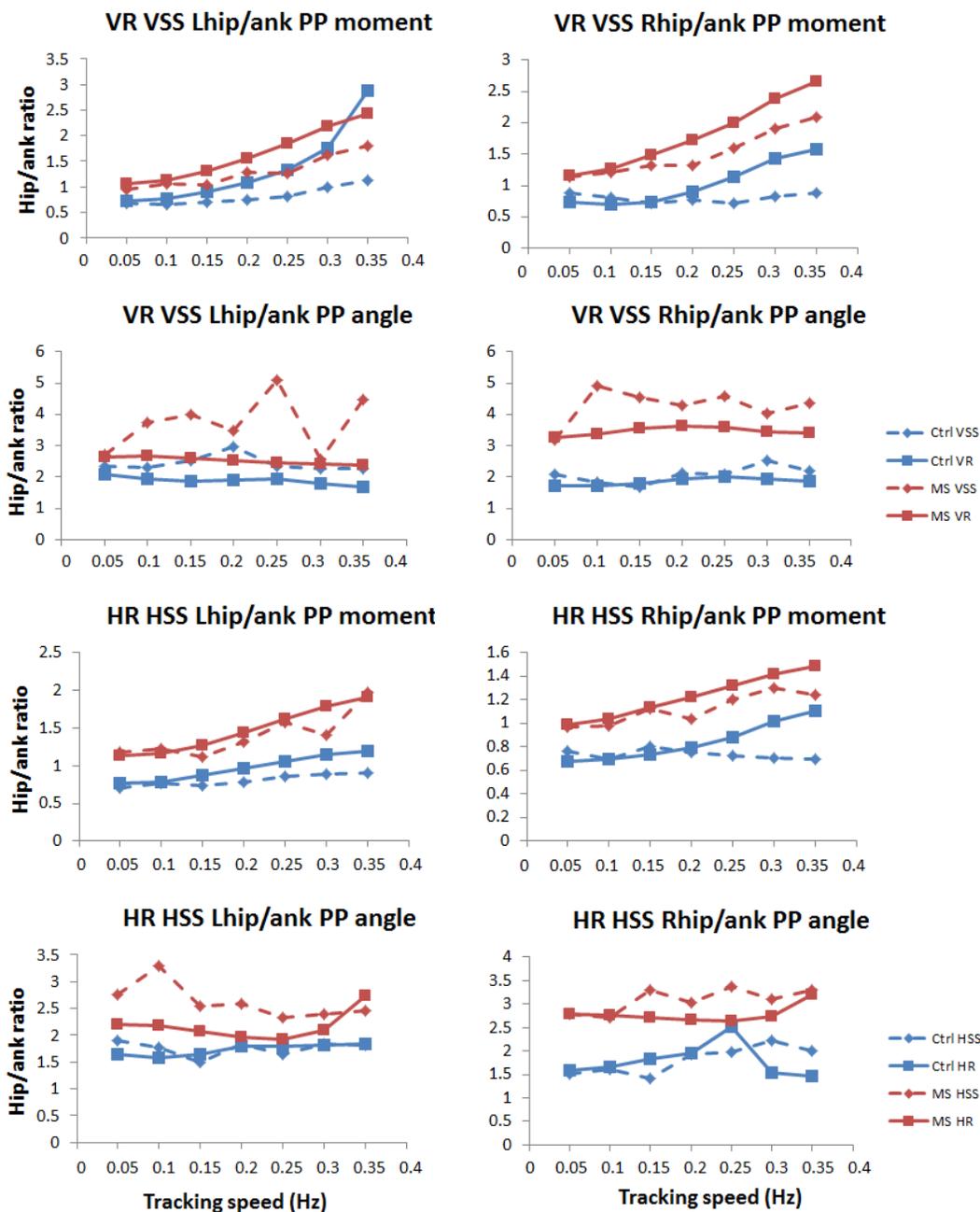


Figure A-1 SS and RS PP Kinematic Parameter For Each Tracking Speed. MS and control group averaged overplots comparing the SS and RS tracking data for the same speeds show that the PP joint moments are larger, while the PP joint angles are slightly smaller during the RS tracking compared to SS tracking.