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Motor Control in Individuals with Multiple Sclerosis

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MOTOR CONTROL IN INDIVIDUALS WITH MULTIPLE SCLEROSIS

by

David J. Arpin

A DISSERTATION

Presented to the Faculty of
the University of Nebraska Graduate College
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for the Degree of Doctor of Philosophy

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Under the Supervision of Professor Max J. Kurz

University of Nebraska Medical Center
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MOTOR CONTROL IN INDIVIDUALS WITH MULTIPLE SCLEROSIS

David J. Arpin, Ph.D.

University of Nebraska, 2016

Supervisor: Max J. Kurz, Ph.D.

This dissertation explored motor control in individuals with multiple sclerosis (MS) by quantifying the behavioral and neurophysiological deficits present in these individuals. We behaviorally quantified the precision of the ankle plantarflexor musculature of individuals with MS. Our results indicated that the individuals with MS had a greater amount of variability in the precision of the isometric ankle torques, and that this greater variability was related to decreased walking performance. To further explore whether these motor control deficits were due to aberrant cortical activity associated with planning motor actions, we used magnetoencephalography to assess the motor planning and execution stages of movement during a goal directed target matching task performed with the knee joint. Interestingly, we found no differences between groups in the cortical activity during the planning and execution stages of movement. However, we did find that individuals with MS had a weaker post-movement beta rebound in the precentral and postcentral gyri relative to healthy controls. These results suggest that the internal model is faulty in individuals with MS. We further explored if the faulty internal model could be due to sensory processing deficits by examining somatosensory gating in these individuals using paired-pulse tibial nerve stimulation. Our results showed reduced somatosensory gating for the individuals with MS, suggesting the inhibitory intracortical circuits may be altered in these individuals. Finally, we examined the cortical responses to single-pulse tibial nerve stimulation at rest and during movement, in order to assess the performance of the sensory system during active movement. Our results indicated that the individuals with MS were unable to properly suppress the

somatosensory responses during movement. All together, the results of this dissertation provide evidence that the impaired motor control of individuals with MS may be due to a faulty internal model, which has become corrupt due to demyelination, and cannot be properly updated due to impaired sensory processing.

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LIST OF ABBREVIATIONS

| | |
|-------------|--|
| CMA | cingulate motor area |
| CNS | central nervous system |
| CSF | cerebrospinal fluid |
| CV | coefficient of variation |
| ECoG | electrocorticography |
| EDSS | Expanded Disability Status Scores |
| EEG | electroencephalography |
| ERD | event-related desynchronization |
| ERS | event-related synchronization |
| fMRI | functional magnetic resonance imaging |
| GABA | gamma-Aminobutyric acid |
| IPS | intraparietal sulcus |
| MEG | magnetoencephalography |
| MRI | magnetic resonance imaging |
| MS | multiple sclerosis |
| MVT | maximum voluntary torque |
| PMBR | post-movement beta rebound |
| PPMS | primary progressive multiple sclerosis |
| RRMS | relapsing-remitting multiple sclerosis |
| SD | standard deviation |

| | |
|-------------|--|
| SEM | standard error of the mean |
| SII | secondary somatosensory cortex |
| SMA | supplementary motor area |
| SMC | primary sensorimotor cortex |
| SPMS | secondary progressive multiple sclerosis |
| TMS | transcranial magnetic stimulation |

INTRODUCTION

Multiple Sclerosis

Multiple sclerosis (MS) is an inflammatory autoimmune disease of the central nervous system (CNS) that results in demyelination of the axons in the brain and spinal cord. This demyelination reduces nerve conduction velocity, impairing the function of the CNS (White & Dressendorfer, 2004). MS has been estimated to affect approximately 570,000 people in the United States (Campbell et al., 2014), and is estimated to cost about \$47,000 per patient per year (Kobelt et al., 2006). The majority of MS diagnoses occur between the ages of 20 and 50 years, with women being about 3 times more likely to be affected than men (Campbell et al., 2014). The exact cause of MS remains unknown, however, it is believed that the disease results from a combination of genetic and environmental factors (Compston & Coles, 2008; Milo & Kahana, 2010).

About 85% of individuals with MS initially present with a relapsing-remitting (RRMS) course, characterized by a sudden appearance of symptoms followed by subsequent improvement (Noseworthy et al., 2000; Keegan & Noseworthy, 2002). Individuals with RRMS typically display a slow deterioration over many years regardless of an acute attack, or relapse. This process typically occurs many years after onset and is termed secondary progressive MS (Keegan & Noseworthy, 2002). Alternatively, MS can present with a primary progressive (PPMS) course, which is characterized by a gradual worsening of symptoms (Noseworthy et al., 2000; Keegan & Noseworthy, 2002).

A number of impairments are commonly associated with MS, including sensory disturbances, gait and balance disorders, cognitive dysfunction, muscle weakness, spasticity, ataxia, fatigue, hypersensitivity to temperature, bladder dysfunction, and visual disturbances. These impairments result from reduced nerve conduction velocity

due the demyelination in the brain and spinal cord (White & Dressendorfer, 2004). While these symptoms vary widely between individuals, approximately 50% of individuals with MS will require the use of a walking aid within 15 years of onset of the disease (Tremlett et al., 2006). Furthermore, approximately 70% of individuals with MS report gait dysfunction to be the most challenging aspect of the disease (LaRocca, 2011).

Historically, the clinical impression was that these mobility impairments were due to weaker muscles that fatigue at a faster rate (Armstrong et al., 1983; Chen et al., 1987; Ponichtera et al., 1992; Rice et al., 1992; Kent-Braun et al., 1997; Lambert et al., 2001). Although this is a likely factor, there has been limited attention to how MS impacts motor control. However, motor control problems that impact the precision of the motor output have been reported in individuals with MS as well (Chen et al., 1987). Although these problems have received limited attention, they may contribute to the larger gait and balance problems reported with MS. Furthermore, the exact cause of these motor control problems is unknown.

Motor control problems can arise due to a break down in any of the processes that occur during the formulation and execution of a motor command. Prior research has established that an internal model of the motor system is used to formulate a motor plan based on sensory feedback, and that this plan is transformed into a motor command (Figure 1; Kurz et al., 2014). Based on this model, dysfunction of any of these stages (i.e., formulation of the motor plan based on the internal model, execution of the motor plan through a sensorimotor transformation, sensory feedback) could lead to the motor control impairments displayed by individuals with MS. Furthermore, it is well known that MS results in alterations to the brain structure, due to tissue damage, as well as functional changes in brain activity, which likely contributes to the impaired motor control.

Neuroimaging in Multiple

Sclerosis

Magnetic resonance imaging (MRI) is the most common brain imaging technique for diagnosing and monitoring the progression of MS, however, there is only a moderate relationship between these structural images and the clinical symptoms (Filippi & Rocca, 2011). This disconnect is likely due to the plasticity and functional reorganization of the brain, which allows individuals, even in advanced stages of the disease, to retain sensory, motor, and cognitive function (Tomassini

et al., 2012; Prosperini et al., 2015). Therefore, the use of functional brain imaging techniques, such as functional MRI (fMRI), has grown in the past few decades. Several of these studies have shown that individuals with MS have diffuse activation across the cortical network compared to healthy adults when performing a simple motor task (Lee et al., 2000; Rocca et al., 2002a; Filippi et al., 2004). Specifically, individuals with MS showed increased activation of the primary sensorimotor cortex (SMC), supplementary motor area (SMA), as well as secondary somatosensory cortex (SII), cingulate motor area (CMA), intraparietal sulcus (IPS), and inferior parietal lobule, among others (Rocca

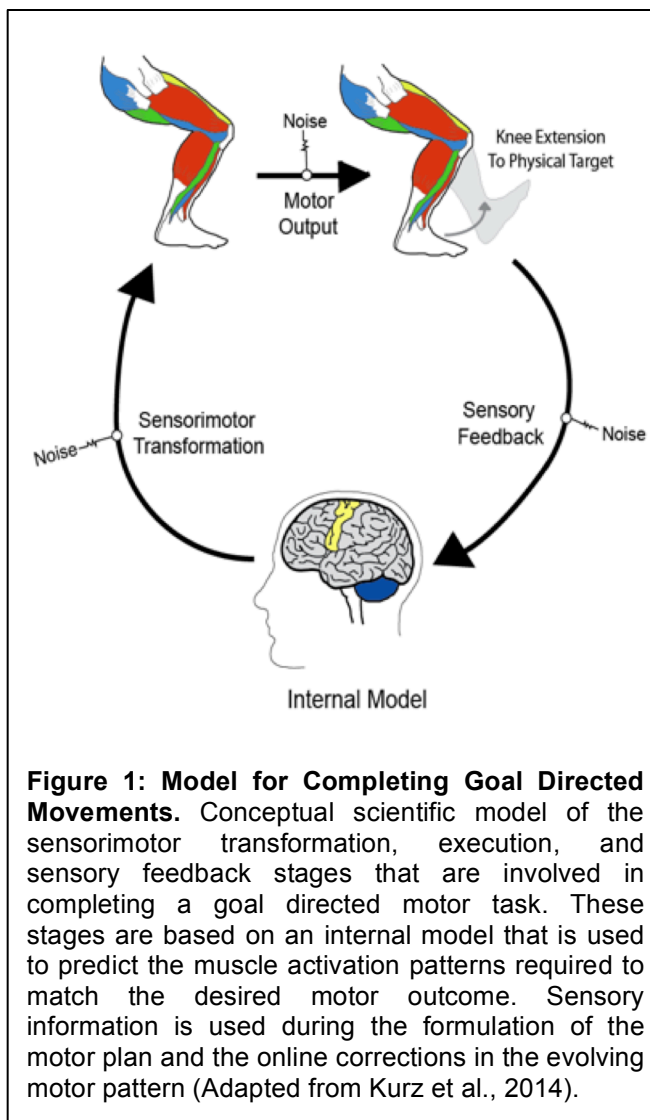


Figure 1: Model for Completing Goal Directed Movements. Conceptual scientific model of the sensorimotor transformation, execution, and sensory feedback stages that are involved in completing a goal directed motor task. These stages are based on an internal model that is used to predict the muscle activation patterns required to match the desired motor outcome. Sensory information is used during the formulation of the motor plan and the online corrections in the evolving motor pattern (Adapted from Kurz et al., 2014).

et al., 2002a; Filippi et al., 2002, 2004). The results from these investigations suggests that the diffuse activation may represent recruitment of other brain areas to overcome the structural tissue damage in the primary cortical areas that would be involved in the motor task. Alternatively, this diffuse activation may represent reduced deactivation of the ipsilateral motor cortex, potentially contributing to the motor control problems seen in these individuals (Manson et al., 2006; Manson et al., 2008). Nevertheless, these results support the notion that the neurological damage incurred by MS may possibly be overcome through the development of new and alternative pathways.

These prior functional neuroimaging studies have primarily focused on simple hand movements, despite the importance of the lower extremity to maintaining a functional gait pattern. However, several studies have assessed functional brain activity in the motor network related to ankle movements (Rocca et al., 2002b; Ciccarelli et al., 2006; Harirchian et al., 2010). These studies have shown increased activation of SII, CMA, and precuneus cortex in individuals with MS during performance of ankle movements (Ciccarelli et al., 2006; Harirchian et al., 2010). Additionally, individuals with MS have shown greater activation of the superior temporal gyrus, rolandic operculum, and putamen in response to passive movement of the ankle (Ciccarelli et al., 2006). This increased activity during passive movements in regions associated with sensorimotor integration suggests that impaired motor control may arise from deficits in sensory processing. Sensory deficits could have a larger impact on the lower extremity than the upper extremity due to the fact that the afferent and efferent information for the leg area of the motor cortex is not as topographically distinct as it is for the upper extremity (Machii et al., 1999).

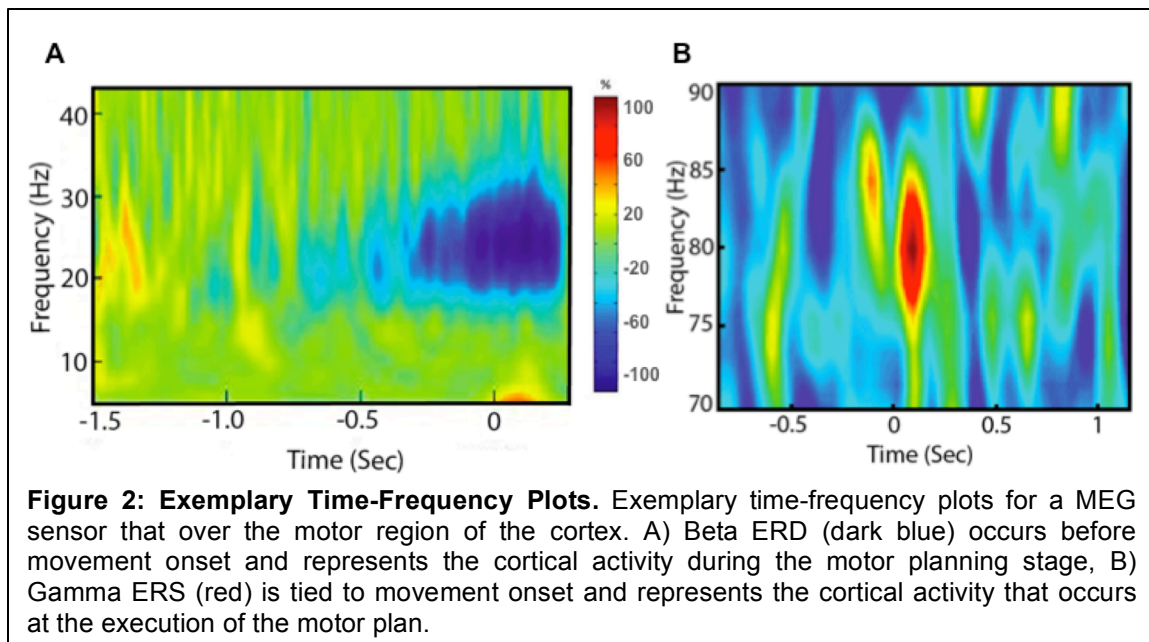
In addition to widespread activation of the sensorimotor network, these studies have suggested that the affected areas are important for motor planning and execution

(Filippi et al., 2002, 2004). Therefore, altered activity within these areas further suggests that the impaired motor control of individuals with MS may be due to deficits in motor planning or execution. However, these speculations cannot be investigated with the current fMRI techniques due to limitations in temporal resolution.

Neural Oscillatory Activity

Neural oscillatory activity in the sensorimotor cortices has been linked to the processes that occur during the planning and execution of movements. Electroencephalography (EEG) and magnetoencephalography (MEG) are currently the only brain imaging techniques with sufficient temporal resolution to assess these neural oscillations. Numerous EEG and MEG experiments have shown that prior to the onset of movement, the cortical oscillatory activity across the sensorimotor cortices decreases in the beta frequency range (15-30 Hz) (Pfurtscheller & Berghold, 1989; Cassim et al., 2000; Kaiser et al., 2001; Alegre et al., 2002; Kilner et al., 2005; Jurkiewicz et al., 2006; Tzagarakis et al., 2010; Wilson et al., 2010, 2011). These results have been confirmed by invasive methods such as subdural electrocorticography (ECoG) in epilepsy patients (Crone et al., 1998; Pfurtscheller et al., 2003; Miller et al., 2007). This decrease in the amount of power found in the beta band frequency, commonly termed beta desynchronization, is thought to reflect task-related changes in the firing rate of local populations of neurons, as they begin to prepare for the specific demands of the pending movement. The consensus is that this beta event-related desynchronization (ERD) is related to the formulation of the motor plan, because it occurs well before the onset of movement, occurs sooner for easier motor tasks, and because the amount of reduction is influenced by the certainty of the movement pattern to be performed (Figure 2A; Kaiser et al., 2001; Alegre et al., 2003; Tzagarakis et al., 2010).

Several invasive ECoG studies have also shown that the beta ERD is followed by an increase (or synchronization) in the high gamma frequency range (>50 Hz) as the motor plan is executed (Crone et al., 1998; Pfurtscheller et al., 2003; Miller et al., 2007). This high frequency activity is restricted to a smaller population of neurons within the primary motor cortex and appears to follow the homuncular organization common in rolandic regions. However, very few EEG investigations have reported high gamma band oscillatory activity during movement because the smaller number of active neuronal generators creates a weaker signal that may be too attenuated by the skull (Pfurtscheller et al., 2003). Furthermore, with EEG there is always a potential for the higher frequencies to become contaminated because they occur at a similar frequency as the head musculature. These measurement problems do not exist in MEG since this technique measures the magnetic fields that naturally emanate from electrical activity in active populations of neurons. The skull does not attenuate the strength or distort magnetic fields, which makes the weaker high-frequency signals readily measurable. Only within the last few years have MEG studies reported gamma-band neural oscillatory activity during movement. The few studies that have been conducted have shown that these gamma band oscillations are closely tied to the onset of muscular activation, and are concentrated in the precentral gyrus (Figure 2B; Cheyne et al., 2008; Wilson et al., 2010, 2011). Based on these initial findings, it has been proposed that the rapid and temporally succinct gamma response initializes the activation of the motor command, which is sent to the relevant motor units. While the central role of beta and gamma neural oscillatory activity during movement is well appreciated, there has been limited effort to use this knowledge to more precisely characterize the motor deficits seen in individuals with MS.



One study has investigated differences in the latency of mu (8-13 Hz) ERD onset in a group of individuals with MS and healthy controls (Leocani et al., 2005). The results showed no significant difference in the latency of mu ERD onset between the two groups. However, when the MS group was subdivided into two groups based on the amount of brain tissue damage, the group with greater tissue damage showed significantly delayed mu ERD onset. This suggests that the disruption of cortico-cortical and cortico-subcortical connections due to tissue damage incurred with MS is related to motor planning deficits (Leocani et al., 2005). Furthermore, evidence suggests deficits in motor planning may also be the origin of fatigue in individuals with MS.

Individuals with MS complaining of fatigue have demonstrated altered frontal and basal ganglia metabolism, measured with positron emission tomography (Roelcke et al., 1997), as well as increased reaction times despite no differences in afferent and efferent conduction velocities between fatigued and rested states (Sandroni et al., 1992). The relationship between fatigue and mu and beta ERD, as well as beta event-related synchronization (ERS), has been explored to assess the link between motor planning

and fatigue (Leocani et al., 2001). Increased beta ERD was found in fatigued individuals with MS compared to nonfatigued individuals with MS and controls. Additionally, postmovement beta ERS was lower in fatigued individuals with MS compared to nonfatigued individuals with MS and controls. Together these results further suggest that motor planning deficits may be related to the fatigue experienced by these individuals. Further exploration of these cortical oscillations will illuminate whether individuals with MS have motor planning deficits, or whether their poor control resides in aberrant sensory feedback or the actual execution of the motor command, or whether all of these alternatives play a significant role.

Current Study

The current study aims to assess the behavioral and neurophysiological deficits present in individuals with MS in order to explore the origin of these motor impairments. To this end, this dissertation presents a series of studies that use a combination of behavioral measures and high-density MEG recording to quantify the motor outcomes and cortical activity of individuals with MS and a group of matched healthy controls. In the first task, we will behaviorally quantify the control of the ankle joint musculature during a steady-state isometric ankle plantarflexion task. In the second task, we will assess the motor planning and execution stages of movement during a goal directed target-matching task performed with the knee joint. In the third task, we will examine the sensory gating response using a paired-pulse tibial nerve stimulation paradigm, which assesses the integrity of the sensory system. Building on this, the fourth task will examine how the sensorimotor cortex responds to single-pulse tibial nerve stimulation during movement and at rest to indicate how the sensory system is performing during movement, and how sensory feedback impacts motor control in individuals with MS. Significant beta ERD and gamma ERS responses will be imaged using beamforming to

examine differences between individuals with MS and healthy adults. We hypothesize that the individuals with MS will have a greater amount of error in the steady-state isometric ankle plantarflexion task, indicating motor control impairment. Furthermore, we hypothesize that the beta ERD and gamma ERS will be reduced prior to and at movement onset respectively in individuals with MS. Finally, we hypothesize that individuals with MS will display altered sensorimotor cortical activity in response to tibial nerve stimulation both at rest and during movement, and that this aberrant cortical activity will be related to behavioral measures of motor control.

CHAPTER 1:REVIEW OF LITERATURE

Epidemiology and Etiology

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) that results in demyelination of the axons in the brain and spinal cord. This demyelination reduces nerve conduction velocity, impairing the function of the CNS (White & Dressendorfer, 2004). MS has been estimated to affect approximately 570,000 people in the United States (Campbell et al., 2014), and is estimated to cost about \$47,000 per patient per year (Kobelt et al., 2006). The majority of MS diagnoses occur between the ages of 20 and 50 years, with women being about 3 times more likely to be affected than men (Campbell et al., 2014).

The prevalence and incidence of MS varies worldwide, but is highest in northern Europe, southern Australia, and the middle part of North America (Noseworthy et al., 2000). The reason for this, and the exact cause of MS remains unknown, however, it is believed that the disease results from a combination of genetic and environmental factors (Compston & Coles, 2008; Milo & Kahana, 2010). Migration studies support the existence of environmental factors by demonstrating that the geographical risk associated with an individual's birthplace is retained if migration occurs after the age of 15 years. However, if an individual migrates before 15 years of age, they assume the risk of their new location (Hammond et al., 2000). Additionally, epidemics of MS have been reported at specific geographic locations and time periods, supporting the idea that exposure to an unidentified infectious agent may predispose individuals to later develop MS (Kurtzke & Hyllested, 1987; Weinshenker, 1996).

The most widely accepted theory is that MS is an autoimmune disease induced by a virus or infection. With this theory, the Epstein-Barr virus, the herpes virus and

chlamydial pneumonia are currently believed to be the mostly likely causes (Herndon, 2003). Examination of the cerebrospinal fluid (CSF) indicates the presence of increased immunoglobulin and oligoclonal bands in 65-95% of MS patients, supporting the theory of an infection causing an autoimmune response, which results in pathological changes (Chelmicka-Schoor & Arnason, 1994). Additionally, viral infections have been shown to precede about 33% of relapses in MS (De Keyser et al., 1998).

Genetics also play a role in the acquisition of MS. Approximately 20% of patients have a family history of MS. The risk is 3-5% for a fraternal twin, but increases to 26% for an identical twin (Sadovnick & Ebers, 1995). Genetic studies have shown multiple genetic markers linked to MS. Specifically, major histocompatibility complex proteins, encoded on chromosome 6, have been linked to antibody production and MS. Evidence suggests that although the disease is not inherited, individuals may inherit a genetic susceptibility to immune system dysfunction (Kahana et al., 1994).

Pathophysiology

MS results in the formation of sclerotic plaque in the nervous system, for which the disease is named. The formation of these plaques involves a number of processes including inflammation, demyelination and remyelination, oligodendrocyte depletion and astrocytosis, and neuronal and axon degeneration (Compston & Coles, 2008). The exact order and the extent to which each of these processes takes place remains unknown. However, it is known that an immune response triggers the production of T-lymphocytes, macrophages, and immunoglobulins. In turn, these cells cross the blood-brain barrier entering the CNS and attack the myelin sheath, which surrounds the nerves. This starts inflammatory processes that signal the release of cytokines and antibodies, causing further breakdown of the blood-brain barrier. Subsequent swelling occurs, along with activation of macrophages, as well as further activation of cytokines and other

destructive proteins (Compston & Coles, 2002). Disruption of the myelin sheath results in demyelination, which slows neural transmission. With severe disruption of the myelin, conduction block occurs, resulting in impaired function. Additionally, local inflammation and infiltrates surround the acute lesion causing abnormally high pressure, which further interferes with the conductivity of the nerve fibers. This inflammation gradually subsides, which may partially account for the fluctuations in function that characterize the disease (Compston & Coles, 2002).

During the early stages of MS the oligodendrocytes can partially repair the myelin through remyelination. However, this remyelination is often incomplete and eventually ceases as the disease progresses and the oligodendrocytes become involved (Chari, 2007). Demyelinated areas eventually are filled with astrocytes, and undergo gliosis, resulting in glial scars, or plaques. At this stage the axon itself is interrupted and undergoes retrograde degeneration. Axonal loss can vary from 10-20% in mild forms of MS, to as much as 80% in more severe forms of the disease (Mews et al, 1998). Axonal damage may have a non-immunological cause, resulting from excitotoxicity due to a compensatory overexpression of sodium and calcium channels, which results from decreased conductivity due to demyelination (Smith, 2007; Patejdl et al., 2016). Additionally, oxidative stress and mitochondrial dysfunction, as well as direct damage from T-lymphocytes may contribute to axonal damage (Patejdl et al., 2016).

Both acute and chronic lesions of varying size can occur anywhere in white or gray matter. These lesions primarily affect white matter in early stages of the disease, with lesions of gray matter evident in more advanced stages. Additionally, other neurodegenerative processes involving the entire CNS take place. These processes include changes in gray matter in the cortex, basal ganglia, brainstem, and spinal cord (Costello, 2008). Brain atrophy also begins in early stages of the disease, and is

believed to be related to disability and progression of the disease (De Stefano et al., 2014). There is also damage or direct dysfunction of oligodendrocytes that produce the myelin (Chari, 2007; Costello, 2008).

Clinical Course

MS is highly variable and unpredictable between patients as well as within a given individual over time. About 85% of individuals with MS initially present with a relapsing-remitting (RRMS) course, characterized by a sudden appearance of symptoms followed by subsequent improvement (Noseworthy et al., 2000; Keegan & Noseworthy, 2002). Individuals with RRMS typically display a slow deterioration over many years regardless of an acute attack, or relapse. This process typically occurs many years after onset and is termed secondary progressive MS (SPMS) (Keegan & Noseworthy, 2002). Alternatively, MS can present with a primary progressive (PPMS) course, which is characterized by a gradual worsening of symptoms (Noseworthy et al., 2000; Keegan & Noseworthy, 2002). Although rare, MS can also present in a benign form, in which the individual remains fully functional, or in a malignant form, which is characterized by rapid onset and progression, leading to significant disability or death within a short time frame. Permanent neurological disability can result from relapse with incomplete remission, progression of the disease, or a combination of the two (Lublin & Reingold, 1996).

Clinical Manifestations

A number of impairments are commonly associated with MS, including sensory disturbances, gait and balance disorders, cognitive dysfunction, muscle weakness, spasticity, ataxia, fatigue, hypersensitivity to temperature, bladder dysfunction, and visual disturbances. These impairments can result from reduced nerve conduction velocity due to the demyelination in the brain and spinal cord (White & Dressendorfer,

2004). While these symptoms vary widely between individuals, and are often not disease-specific, Lhermitte's symptom and Uhthoff's symptom are characteristic of multiple sclerosis. Lhermitte's symptom is the sensation of an electric shock running down the spine and into the lower extremities, whereas Uhthoff's symptom is a temporary worsening of symptoms when the individual's body temperature increases (Compston & Coles, 2008).

Gait and balance impairments are another notable symptoms of MS. Approximately 50% of individuals with MS will require the use of a walking aid within 15 years of onset of the disease (Tremlett et al., 2006). Historically, the clinical impression was that these mobility impairments were due to weaker muscles that fatigue at a faster rate (Armstrong et al., 1983; Chen et al., 1987; Ponichtera et al., 1992; Rice et al., 1992; Kent-Braun et al., 1997; Lambert et al., 2001). Additionally, studies have reported a higher proportion of type II muscle fibers due to disuse atrophy (Kent-Braun et al., 1997). Although these are likely factors contributing to the motor impairments seen in these individuals, there has been limited attention to how MS impacts motor control.

Studies have reported reduced firing rates of the motor units and/or an inability to fully activate the available motor units in individuals with MS (Dorfman et al., 1989; Rice et al., 1992). Additionally, motor control problems that impact the precision of the motor output have been reported in individuals with MS as well (Chen et al., 1987). Although motor control problems have received limited attention, evidence suggests that they contribute to the larger gait and balance problems reported with MS (Davies et al., 2015). Unfortunately, the exact cause of these motor control problems remains unknown.

Neuroimaging in Multiple Sclerosis

Structural neuroimaging

Magnetic resonance imaging (MRI) is the most common brain imaging technique for diagnosing and monitoring the progression of MS. T2-weighted MRIs are commonly used to measure total lesion volume. In individuals with RRMS and SPMS, total lesion volume increases by about 5-10% per year (Paty et al., 1994). However, the strength of the correlation between T2-hyperintense lesion burden and disability is rather low (Filippi & Rocca, 2007). This disconnect is likely due to the limitations of the clinical scales used to measure impairment and disability in these individuals, as well as the inability of conventional MRI to characterize and quantify the severity of MS (Bakshi et al. 2008).

Cortical lesions are typically difficult to detect on conventional MRIs because they are relatively small, have poor contrast against the surrounding gray matter, and can be obscured by partial volume effects from CSF (Filippi & Rocca, 2007, 2011). However, double-inversion-recovery magnetic resonance sequences can suppress the signal from the white matter and CSF to significantly improve the ability of MRI to depict cortical lesions (Filippi & Rocca, 2011). Relationships between cortical lesion burden and progression of disability have been found (Calabrese et al., 2009b; Calabrese et al., 2010a), as well as between cortical lesion burden and severity of cognitive impairment (Calabrese et al., 2009a; Roosendaal et al., 2009). However, it is important to note that this MRI technique has a number of limitations, including a low signal-to-noise ratio among others, thus the ability to detect cortical lesion in individuals with MS remains problematic (Filippi & Rocca, 2011).

Imaging studies have also found that brain volume decreases by about 1% per year in individuals with MS, measured using T1-weighted MRI sequences (Miller et al.,

2002). These brain atrophy measures appear to be more pathologically specific than T2 lesion load measures, however, they are still only moderately correlated with disability measures in individuals with RRMS and SPMS (Miller et al., 2002; Giorgio et al., 2008). Atrophy of specific areas has been suggested to help explain specific disease-related symptoms. For instance, atrophy of the hippocampus has been related to memory deficits (Sicotte et al., 2008), while atrophy of the frontal and parietal lobes has been related to fatigue (Sepulcre et al., 2009; Pellicano et al., 2010).

Functional Neuroimaging

Plasticity and functional reorganization of the brain, even in advanced stages of the disease, likely allow individuals with MS to retain sensory, motor, and cognitive function (Tomassini et al., 2012; Prosperini et al., 2015). This likely contributes to the poor relationships reported between structural brain images and the clinical symptoms (Filippi & Rocca, 2011). Therefore, the use of functional brain imaging techniques, such as functional magnetic resonance imaging (fMRI), has grown in the past few decades.

Several fMRI studies have shown that individuals with MS have diffuse activation across the cortical network compared to healthy adults when performing a simple motor task (Lee et al., 2000; Rocca et al., 2002a; Filippi et al., 2004). Specifically, individuals with MS showed increased activation of the primary sensorimotor cortex (SMC), supplementary motor area (SMA), as well as secondary somatosensory cortex (SII), cingulate motor area (CMA), intraparietal sulcus (IPS), and inferior parietal lobule, among others (Rocca et al., 2002a; Filippi et al., 2002, 2004). The results from these investigations suggests that the diffuse activation may represent recruitment of other brain areas to overcome the structural tissue damage in the primary cortical areas that would be involved in the motor task. Alternatively, this diffuse activation may represent reduced deactivation of the ipsilateral motor cortex, potentially contributing to the motor

control problems seen in these individuals (Manson et al., 2006; Manson et al., 2008). Nevertheless, these results support the notion that the neurological damage incurred by MS may possibly be overcome through the development of new and alternative pathways.

The development of this cortical reorganization has been explored in a cross-sectional study (Rocca et al., 2005). Early in the disease course increased recruitment is seen in cortical areas devoted to the performance of a motor task, such as the SMC and SMA. Subsequently, bilateral activation of these regions is evident. Finally, in later stages of the disease, activation of additional brain areas, which are normally recruited to perform novel or complex tasks in healthy individuals, is seen (Rocca et al., 2005).

Evidence also exists supporting the idea that the functional changes seen in individuals with MS may be maladaptive. Several studies have found reduced activation of the sensorimotor network and increased activation of higher order brain areas, such as the superior temporal sulcus and the insula, when performing a motor task (Rocca et al., 2002b, 2010). Potentially, this may suggest that at a given threshold the brain is unable to continue to reorganize and compensate for the tissue damage.

These prior functional neuroimaging studies have primarily focused on simple hand movements, despite the importance of the lower extremity to maintaining a functional gait pattern and the known mobility impairments in individuals with MS. However, several studies have assessed functional brain activity in the motor network related to ankle movements (Rocca et al., 2002b; Ciccarelli et al., 2006; Harirchian et al., 2010). These studies have shown increased activation of SII, CMA, and precuneus cortex in individuals with MS during performance of ankle movements (Ciccarelli et al., 2006; Harirchian et al., 2010). Additionally, individuals with MS have shown greater activation of the superior temporal gyrus, rolandic operculum, and putamen in response

to passive movement of the ankle (Ciccarelli et al., 2006). This increased activity during passive movements in regions associated with sensorimotor integration suggests that impaired motor control may arise from deficits in sensory processing. Sensory deficits could have a larger impact on the lower extremity than the upper extremity due to the fact that the afferent and efferent information for the leg area of the motor cortex is not as topographically distinct as it is for the upper extremity (Machii et al., 1999).

In addition to widespread activation of the sensorimotor network, these studies have suggested that the affected areas are important for motor planning and execution (Filippi et al., 2002, 2004). Therefore, altered activity within these areas further suggests that the impaired motor control of individuals with MS may be due to deficits in motor planning or execution. However, these speculations cannot be investigated with the current fMRI techniques due to limitations in temporal resolution.

Electroencephalography (EEG) and magnetoencephalography (MEG) are currently the only brain imaging techniques with sufficient temporal resolution to assess the neural processes that occur during the planning and execution of movements. Numerous EEG and MEG experiments have shown that prior to the onset of movement, the neural oscillatory activity within the sensorimotor cortices decreases in the beta frequency range (15-30 Hz) (Jurkiewicz et al., 2006; Cheyne et al., 2006, 2008; Gaetz et al., 2010; Muthukumaraswamy, 2010; Heinrichs-Graham et al., 2014; Kurz et al., 2014; Wilson et al., 2014; Tzagarakis et al., 2015). This decrease in the amount of power found in the beta band frequency, commonly termed beta desynchronization, is thought to reflect task-related changes in the firing rate of local populations of neurons, as they begin to prepare for the specific demands of the pending movement. This beta event-related desynchronization (ERD) is thought to be related to the formulation of the motor plan. However, there has been limited effort to use this knowledge to more precisely

characterize the motor deficits seen in individuals with MS.

One study has investigated differences in the latency of mu (8-13 Hz) ERD onset in a group of individuals with MS and healthy controls (Leocani et al., 2005). The results showed no significant difference in the latency of mu ERD onset between the two groups. However, when the MS group was subdivided into two groups based on the amount of brain tissue damage, the group with greater tissue damage showed significantly delayed mu ERD onset. This suggests that the disruption of cortico-cortical and cortico-subcortical connections due to tissue damage incurred with MS is related to motor planning deficits (Leocani et al., 2005). Furthermore, evidence suggests deficits in motor planning may also be the origin of fatigue in individuals with MS.

Individuals with MS complaining of fatigue have demonstrated altered frontal and basal ganglia metabolism, measured with positron emission tomography (Roelcke et al., 1997), as well as increased reaction times despite no differences in afferent and efferent conduction velocities between fatigued and rested states (Sandroni et al., 1992). The relationship between fatigue and mu and beta ERD, as well as beta event-related synchronization (ERS), has been explored to assess the link between motor planning and fatigue (Leocani et al., 2001). Increased beta ERD was found in fatigued individuals with MS compared to nonfatigued individuals with MS and controls. Additionally, postmovement beta ERS was lower in fatigued individuals with MS compared to nonfatigued individuals with MS and controls. Together these results further suggest that motor planning deficits may be related to the fatigue experienced by these individuals.

Fatigue

Up to 90% of individuals with MS are affected by fatigue, even in early stages of the disease (Riccitelli et al., 2011). Furthermore, individuals with MS report fatigue as the

symptom that interferes most with their daily activities (Kesselring & Beer, 2005). Despite this, the few medications available for the treatment of MS fatigue have limited efficacy and can present various side effects (Kesselring & Beer, 2005).

Fatigue comes on abruptly and resembles an overwhelming flu-like exhaustion. The severity of disease does not appear to be related to fatigue severity, as individuals with mild symptoms report disabling fatigue as often as more affected individuals (Fisk et al., 1994). Fatigue has also been associated with a number of disease-related factors, including sleep disorders, depression, anxiety, level of neurologic disability, and disease course (Mills & Young, 2011). There are also psychosocial factors contributing to fatigue, as individuals with a low sense of environment mastery, or sense of control, report significantly greater fatigue (Schwartz et al., 1996). Together these factors make it difficult to determine the underlying cause of fatigue in individuals with MS.

Numerous hypotheses have been proposed to explain the causes of fatigue, however, the high variability and subjective nature of the symptoms makes it difficult to determine the underlying cause. One hypothesis is that fatigue arises due to the chronic inflammation associated with MS. However, studies assessing the relationship between cytokines and other biomolecules that are released throughout the course of inflammation and self-reported measures of fatigue do not support this idea (Patejdl et al., 2016). Another hypothesis is that fatigue is related to the cortical reorganization and plasticity that occurs in individuals with MS. In theory, the fastest and most direct connections between cortical regions are lost, requiring in the integration of more cortical areas as compensation in order to perform motor or cognitive tasks (Patejdl et al., 2016). This process reduces the information processing capacity and increases metabolic requirements, potentially resulting in fatigue (Reddy et al., 2000). Furthermore, this hypothesis seems to be supported by neuroimaging studies that show widespread

activation of the sensorimotor network, including areas that are important for motor planning and execution (Filippi et al., 2002, 2004).

It has also been hypothesized that MS related fatigue may occur due to altered cortical excitability and neurotransmission. Transcranial magnetic stimulation (TMS) is often used to assess neural excitability by noninvasively stimulating a specific area of the brain. In doing so, the motor threshold, or the lowest TMS stimulation intensity required to elicit a muscle response, can be used as an indication of the neural excitability, number of corticomotor neurons and/or strength of corticospinal projection. Similarly, the size of the motor evoked potential can also reflect neural excitability. Finally, the central motor conduction time can also be determined by subtracting the latency of the spinal motor neuron to the muscle from the latency of the cortex to the muscle (Yusuf & Koski, 2013). Several studies have used these techniques, however, they do not appear to be related to self-reported fatigue measure (Yusuf & Koski, 2013).

Several studies have also examined muscle fatigue by assessing decreases in task performance or measuring the time until the subject can no longer successfully complete the task. The outcomes of these studies, however, have been mixed. Some studies have found that individuals with MS fatigue more quickly than healthy controls and that the decreased time to fatigue is related to self-reported measures of fatigue (Petajan & White, 2000; Liepert et al., 2005). However, others have found no differences in the time to fatigue, contractile force, or speed of the task (Perretti et al., 2004; Thickbroom et al., 2006, 2008). Potentially, the mixed outcomes of these studies may be due to the intensity of the exercise being performed, as the tasks consisted of submaximal contractions (Yusuf & Koski, 2013).

To assess neurophysiological changes accompanying muscular fatigue in individuals with MS, central drive and motor force production have been examined

during fatiguing motor tasks. Central drive to the muscle is measured as a proportion of the total electrically stimulated twitch force that can be accounted for by central rather than peripheral mechanisms (Yusuf & Koski, 2013). Studies in patients with RRMS or groups of patients with different disease courses have found greater decline in central drive during exercise in individuals with MS compared to healthy controls (Sheean et al., 1997, 1998). Additionally, decline in central drive during exercise is related to a greater decline in maximal voluntary contractile force in individuals with MS (Sheean et al., 1997; Romani et al., 2004). Therefore, changes in central drive appear to be an important component of fatigue in individuals with MS. However, central fatigability is not likely to be the primary explanation for fatigue symptoms, because it is not related to patient-reported measures of fatigue severity (Sheean et al., 1997; Romani et al., 2004). Thus, the underlying causes of fatigue remain difficult to identify.

CHAPTER 2: MULTIPLE SCLEROSIS INFLUENCES THE PRECISION OF THE ANKLE PLANTARFLEXION MUSCULAR FORCE PRODUCTION^a

Introduction

Multiple sclerosis (MS) is a demyelinating disease that occurs in young adults and often affects the control of the leg musculature. Numerous individuals with MS experience mobility and balance impairments that limit their activities of daily living (Ellis & Motl, 2013). Historically, the clinical impression was that these impairments were due to weaker muscles that fatigue at a faster rate (Armstrong et al., 1983; Chen et al., 1987; Ponichtera et al., 1992; Rice et al., 1992; Kent-Braun et al., 1997; Lambert et al., 2001). Although this is likely a factor, there has been limited attention to how MS impacts the precision of the ankle musculature control. Precise control of the ankle joint is important for correcting the postural sway, clearing the foot during the swing phase of gait and push-off at terminal stance (Horak & Nashner, 1986; Winter, 1991). It has been shown that individuals with MS with higher Kurtzke Expanded Disability Status Scores (EDSS) tend to generate less power by the ankle joint during the stance phase of gait (Huisinga et al., 2013). Additionally, spasticity in the gastrocnemius and soleus muscles has been shown to impact the gait and balance in individuals with MS (Sosnoff et al., 2011). Taken together, these results suggest that a reduction in control of the ankle joint musculature may be a primary factor that leads to the mobility and balance impairments seen in individuals with MS.

Variability or error is present in all voluntary contractions and impacts the precision and control of the motor performance (Hamilton et al., 2004; Kouzaki &

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Shinohara, 2010; Kwon et al., 2012). Several investigations have shown that aging results in greater variability in the steady-state isometric performance of the ankle joint, and that these variations may be a result of the inability to properly activate the motor unit pool that innervates the ankle musculature (Sosnoff et al., 2011; Kwon et al., 2012). Despite this insight, limited efforts have been made to determine if MS further amplifies the amount of variability that occurs while attempting to control the precision of the ankle musculature. A previous study has shown that individuals with MS may have an increased amount of variability in motor unit firing rate (Dorfman et al., 1989). Given that the variability of the motor unit discharge rate is known to be associated with increased force variability during isometric force tasks (Enoka et al., 2003), it is possible that individuals with MS may display an increased variability while trying to control the precision of the muscular force. Potentially, a greater amplification of the variability at the ankle joint may be a key factor for the mobility impairments often reported in individuals with MS.

The primary purpose of this study was to quantify the amount of variability or error in the precision of the steady-state ankle plantarflexion isometric muscular forces generated by individuals with MS. We hypothesized that 1) compared with controls, individuals with MS will have an amplified amount of variability when they attempt to precisely match a low level isometric target with their ankle plantarflexors. Secondly, we hypothesized that 2) individuals with MS will have weaker isometric ankle plantarflexion muscular strength, 3) the spatiotemporal gait kinematics will be altered, and 4) the spatiotemporal gait kinematics will be related to the amount of variability seen in the precision of the ankle plantarflexor target matching task.

Methods

Twenty-two adults (Age: 49.3 ± 8 years; Female = 14) with relapsing-remitting or secondary progressive MS participated in the study. The subjects had an average EDSS of 5.3 ± 1 (median = 5.75), which indicates that on average each subject could walk independently for at least 100 meters with an assistive device (e.g., cane). Twenty normal, healthy adults served as a control group (Age: 45.1 ± 14 years; Female = 16). All testing was done at the University of Nebraska Medical Center. This study was approved by the Institutional Review Board and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Additionally, all participants provided informed consent prior to participation in the study.

The subjects performed the isometric ankle plantarflexion contractions seated in an isokinetic dynamometer (Biodex Inc., Shirley, NY). The chair of the isokinetic dynamometer had the backrest set at an angle of 90° , and the participant had their knee fully extended with their ankle in a neutral position. A foot strap was used to secure their foot to the metal footplate. The largest torque generated from two maximum isometric contractions was used to establish the participant's maximum voluntary torque (MVT) and was normalized by body weight (kg) prior to comparison. For the experiment, the participant performed two steady-state isometric contractions at 20% of their MVT. The target and the torque exerted by the participant was displayed as a bar graph on a large monitor that was positioned ~ 1 meter away from the subject at eye level. The participant was instructed to produce and hold a plantarflexion force that matched the 20% MVT target. The participant was given ample time to practice achieving the target torque before the two actual trials were recorded. These two trials were then averaged together for all data measures. The voltage output from the torque motor was read by custom LabVIEW (National Instrument Inc., USA) software and sampled at 1 kHz by a 14-bit

National Instruments analogue-to-digital converter. The voltage output from the Biodex dynamometer was converted to Nm and displayed in real-time to the participant. The maximum on the vertical scale of the bar graph was twice the target value (Kouzaki & Shinohara, 2010). Each steady-state contraction was performed for 30 seconds. The coefficient of variation ($CV = [\text{Standard Deviation of Torque}/\text{Mean Torque}] \times 100$) was used to assess the amount of variability present in the middle 15 seconds of the steady-state torque. A greater CV value was an indication of a larger amount of error in the joint steady-state torque control (Christou & Tracy, 2006).

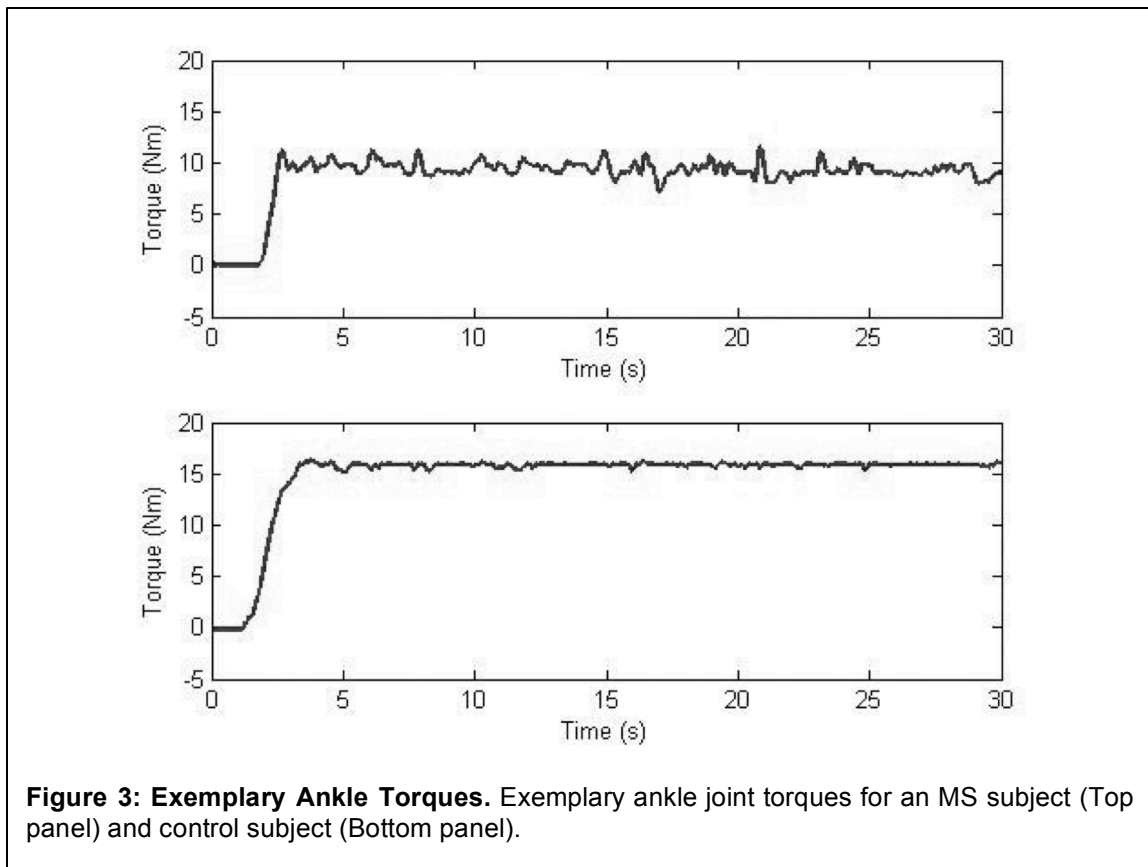
Prior to the completion of the ankle plantarflexion task described above, the participants walked across a digital mat (GaitRITE, Sparta, NJ) at their preferred and fast-as-possible walking speeds. The mat quantified the participant's spatiotemporal kinematics and was used to calculate the walking velocity, step width, step length, cadence. In addition, the standard deviation of the step length, and step width were used to quantify the gait variability. Each participant completed two walking trials at the respective speeds and the data from these two trials was averaged together.

Independent t-tests were used to examine the differences between the MS and control groups for the maximum torque, CV and the spatiotemporal kinematics. Spearman rho correlations were used to evaluate the relationship between the CV of the steady-state torque and the spatiotemporal kinematics, as well as MVT and the spatiotemporal kinematics. All statistical analyses were conducted using SPSS version 22 (IBM, Armonk, NY), with an alpha level of 0.05.

Results

A representative time series for an individual with MS and a control performing the ankle plantarflexion motor task is shown in Figure 3. Qualitatively it is apparent that

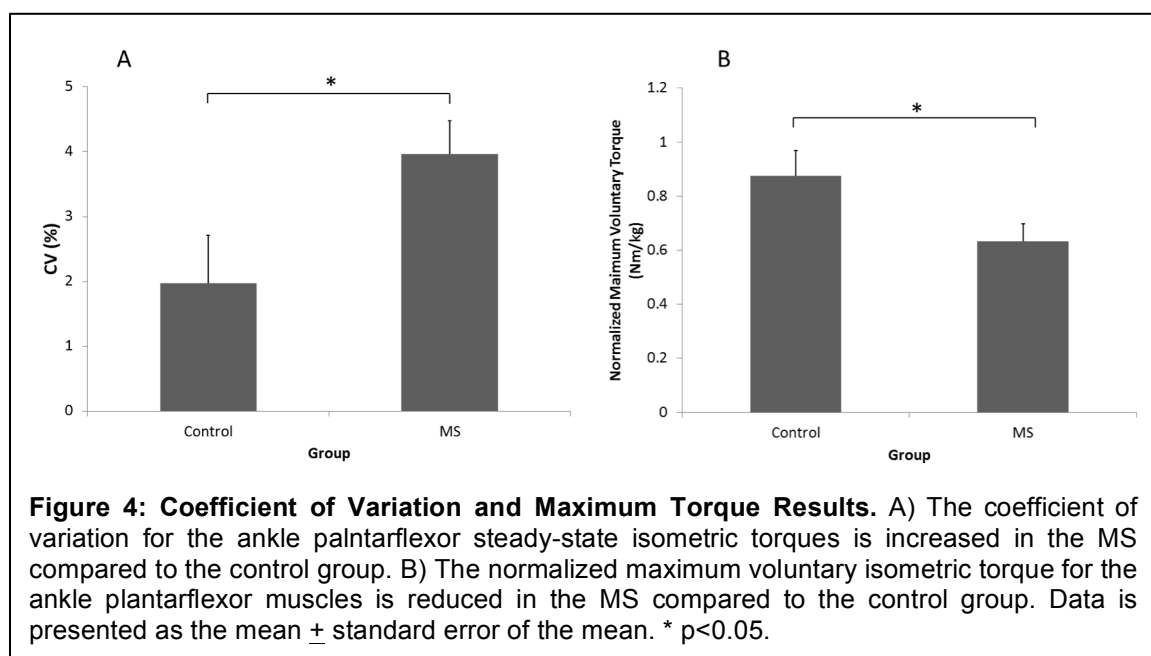
the individual with MS had greater variability when trying to control the precision of the ankle joint plantarflexor musculature. This observation was confirmed by the CV for the steady-state torques, where the CV was greater for the individuals with MS compared to the controls ($p = 0.03$; Figure 4A). Hence, indicating that the participants with MS



generated more errors when attempting to control the precision of their ankle plantarflexor muscular force production. The maximum torque generated by the ankle plantarflexors was also significantly lower for the individuals with MS compared with the controls ($p = 0.03$; Figure 4B). This indicated that the individuals with MS also had weaker isometric ankle plantarflexor strength compared to the controls.

The spatiotemporal gait kinematics were notably different between the two groups for all variables. At preferred walking speeds, the individuals with MS had a slower walking velocity (MS = 0.68 ± 0.22 m/s, controls = 1.28 ± 0.14 m/s; $p < 0.01$),

wider step width (MS = 0.16 ± 0.04 m, controls = 0.11 ± 0.02 m; $p < 0.01$), shorter step length (MS = 0.44 ± 0.08 m, controls = 0.67 ± 0.07 m; $p < 0.01$), and slower cadence (MS = 92.2 ± 21.4 steps/min, controls = 114.5 ± 9.4 steps/min; $p < 0.01$). In addition, the step lengths (MS = 3.39 ± 1.81 cm, controls = 1.91 ± 0.86 cm; $p < 0.01$), and step widths (MS = 2.81 ± 1.39 cm, controls = 1.74 ± 0.92 cm; $p = 0.02$) were more variable in the MS group.



The same was true at fast-as-possible walking speeds, with individuals with MS having a slower velocity (MS = 0.93 ± 0.36 m, controls = 1.98 ± 0.27 m; $p < 0.01$), wider step width (MS = 0.14 ± 0.04 m, controls = 0.10 ± 0.03 m; $p < 0.01$), shorter step length (MS = 0.51 ± 0.12 m, controls = 0.80 ± 0.09 m, $p < 0.01$), slower cadence (MS = 109.8 ± 28.7 steps/min, controls = 148.4 ± 16.3 steps/min, $p < 0.01$). The step length (MS = 3.45 ± 1.97 cm, controls = 2.29 ± 1.49 cm; $p = 0.04$), and step width (MS = 2.54 ± 0.98 cm, controls = 1.86 ± 0.79 cm; $p = 0.02$) continued to be more variable for the MS group at the fast-as-possible walking speed.

There were moderate negative correlations between the CV of the steady-state torque and the preferred walking velocity ($r = -0.48$, $p < 0.01$), step length ($r = -0.46$, $p < 0.01$), and cadence ($r = -0.31$, $p = 0.04$). We also found moderate negative correlations between the CV of the steady-state torque and the fast-as-possible walking velocity ($r = -0.52$, $p < 0.01$), step length ($r = -0.48$, $p < 0.01$), and cadence ($r = -0.45$, $p < 0.01$). Altogether these correlations imply that a reduce precision of the control of the ankle plantarflexor musculature force production may be partially related to a slower walking speed and altered spatiotemporal kinematics.

We also found weak but positive correlations between the MVT and the preferred walking velocity ($r = 0.35$, $p = 0.03$) and step length ($r = 0.37$, $p = 0.02$). The same was true for the fast-as-possible walking speed where there was a weak to moderate positive correlations between the MVT and walking velocity ($r = 0.52$, $p < 0.01$), step length ($r = 0.46$, $p < 0.01$), and cadence ($r = 0.37$, $p = 0.02$). This suggests that weakness in the ankle plantarflexors may also be partially related to the slower walking speed and altered spatiotemporal kinematics of individuals with MS.

Finally, there were weak but positive correlations between the CV of the steady-state torque and the variability of the step length ($r = 0.36$, $p = 0.02$) and step width ($r = 0.34$, $p = 0.03$) during preferred walking speeds, as well as the variability of the step width ($r = 0.43$, $p = 0.01$) during fast-as-possible walking speeds. These correlations imply that poor control of the ankle musculature may partly contribute to the increased gait variability seen in individuals with MS.

Discussion

Our results show that individuals with MS have an amplified amount of variability or errors when attempting to control the precision of the force production of the ankle

plantarflexor musculature. Comparable results have been previously reported for sustained short duration knee maximal isometric contractions for individuals with MS (Horak & Nashner, 1986). Taken together, these results indicate that individuals with MS have greater errors when attempting to control of the precision of the lower extremity musculature. Prior electroencephalography (EEG) studies have eluded that the neurologic injury caused by MS to the central nervous system may impact the cortical activation that that is associated with planning motor actions (Leocani et al., 2001; Leocani et al., 2005). Transcranial magnetic stimulation (TMS) studies have also shown that the transmission of the motor command along the corticospinal tracts is delayed in persons with MS (Gagliardo et al., 2007; Kale et al., 2009). Based on these neurophysiological outcomes, it is likely that the heightened variability seen in the ankle plantarflexion muscular performance reflects the extent of the damage within the corticospinal fiber tracts and/or the sensorimotor cortices.

The MVT for the ankle plantarflexors was lower for the individuals with MS, indicating that the participants with MS had strength deficits. This result concurs with what has been well established in the literature (Armstrong et al., 1983; Chen et al., 1987; Ponichtera et al., 1992; Rice et al., 1992; Kent-Braun et al., 1997; Lambert et al., 2001; Wagner et al., 2014). Weaker muscles are known to have more noise in their isometric force production (Hamilton et al., 2004); therefore, it is possible that the greater amount of error seen in the precision of the ankle isometric force production of the individuals with MS may partially be a result of the inability to suppress these stochastic features. Potentially, demyelination may not only promote weakness, but also allows for the biological noise to further infiltrate the intended motor output.

Our results also showed that individuals with MS had a slower walking velocity, wider step width, shorter step length, and slower cadence at both preferred and fast-as-

possible walking speeds. Prior studies have shown similar alterations to the spatiotemporal gait kinematics of individuals with MS (Benedetti et al., 1999; Kelleher et al., 2010). Additionally, we found negative correlations between the CV of the steady-state torque and velocity, step length, and cadence for both the preferred and fast-as-possible walking speeds. This suggests that a greater amount of variability or error in the precision of the ankle plantarflexion force was related to a slower walking velocity, a shorter step length and a slower cadence. Therefore, these results imply that the mobility deficits seen in participants with MS may have been related to a reduction in the control of the precision of the ankle musculature force production.

There were positive correlations between the strength of the ankle plantarflexors and preferred walking velocity and step length. In addition, there were complementary positive correlations between the strength of the ankle plantarflexors and the fast-as-possible walking velocity, step length and cadence. This suggests that weakness in the ankle plantarflexors is likely also related to slower walking velocity and altered spatiotemporal kinematics. Prior research has shown that resistance training protocols targeting the lower extremities improves the strength of the ankle joint musculature, as well as the gait kinematics of individuals with MS (White et al., 2004; Gutierrez et al., 2005). Together these results imply that the mobility deficits seen in individuals with MS may be partially related to strength deficits as well as deficits in the control of the ankle musculature.

Our results also showed that individuals with MS had greater variability in the step length and step width during both preferred and fast-as-possible walking speeds. Increased gait variability is known to exist in individuals with MS; however the mechanisms contributing to this variability remains poorly understood (Socie & Sosnoff, 2013; Kaipust et al., 2012; Socie et al., 2013, 2014). Likely there are combinations of

possible factors that contribute to increased gait variability, as variability in the gait pattern may arise from a breakdown in any of the numerous neural processes. Our results suggest that poor control of the ankle musculature may be partially related to the heightened gait variability seen in individuals with MS. However, we are somewhat cautionary to state that the gait variability is primarily due to poor control of the ankle joint because the strength of our correlations were relatively weak, which suggests that other factors likely play a more prominent role (i.e., spasticity, fatigue). Prior research has shown that a large number of steps are necessary to accurately quantify gait variability (Owings & Grabiner, 2003). Therefore, it is alternatively possible that the weak correlations seen here may be due to the inability of a few steps to accurately capture the gait variations seen in our participants.

Interventions aimed at improving the control of the ankle joint in individuals with MS have been limited; however, the few studies that have been conducted have shown improvements in ankle joint function following therapeutic intervention. Huisinga and colleagues have shown improvements in the dynamic joint torques produced by the ankle during the stance phase of gait in individuals with MS following an elliptical exercise intervention (Huisinga et al., 2012). Additionally, prior studies have shown improvements in strength and alterations in the interference EMG after individuals with MS complete a strength training program (Fimland et al., 2010; Dalgas et al., 2013). Taken together, these studies suggest that therapeutic interventions can potentially improve the control of the ankle muscular force production and strength of individuals with MS. Potentially, such improvements may also reduce the amount of error in the precision of the muscular force production of the ankle plantarflexors, which may lead to improvements in balance and mobility.

There are several limitations to this study. Although we have shown that individuals with MS exhibit a greater amount of variability or errors in the precision of their isometric plantarflexion forces at 20% MVT, it remains unknown how control of the plantarflexor musculature changes with varying force levels or during a dynamic isokinetic force matching tasks. The steady-state isometric target matching task used in this study likely does not approximate the ankle control required during gait, which may explain why the correlations we found between the CV and the spatiotemporal gait kinematics were moderate. Additionally, it is possible that the greater variability seen in the precision of the muscular force production of individuals with MS may have been related to possible visuomotor impairments, as these are common in individuals with MS. Thus, it is plausible that the larger variability in force production in individuals with MS may be due to a need to see larger changes in the visual feedback in order to make corrections. Finally, with this study we are unable to identify the specific underlying neurophysiological mechanisms that may be responsible for the heightened variability in the precision of the ankle plantarflexor musculature force production.

Conclusion

Our results show that individuals with MS have an amplified amount of variability when attempting to control the precision of the force production of the ankle plantarflexor musculature. These precision errors appear to be partially related to the extent of the impairments seen in the walking speed, spatiotemporal kinematics and gait variability of individuals with MS. These results further fuel the impression that a reduction in control of the ankle joint musculature may be a key factor in the mobility and balance impairments seen in individuals with MS.

CHAPTER 3: ALTERED SENSORIMOTOR CORTICAL OSCILLATIONS IN INDIVIDUALS WITH MULTIPLE SCLEROSIS SUGGESTS A FAULTY INTERNAL MODEL

Introduction

Multiple sclerosis (MS) is a demyelinating disease that impacts the function of the central nervous system, and often results in impaired muscular performance. Previously, we have shown that individuals with MS have greater errors when attempting to control the precision of the lower extremity force production (Davies et al., 2015; Arpin et al., 2016). While these results are insightful, the neurophysiological abnormalities that may be responsible for the reduced muscular force control remains unknown. Potentially, the errors in the precision of the force production may partly be a result of imperfections in the internal model that is used to make accurate predictions of the motor output that will meet the task demands.

Prior research has established that the brain maintains and updates an internal model that is used to predict the muscular synergies necessary to achieve a motor goal (Kording et al., 2004; Shadmehr, 2004; Wolpert, 2007). This internal model is used to formulate a motor plan based on sensory feedback and knowledge of results from prior attempts to achieve the motor goal. The motor plan is then transformed into a motor command, which contains the predicted muscular synergies required to achieve the motor goal. Once the motor command is executed, the sensory feedback that occurs can then be compared with the sensory feedback expected by the internal model. Any mismatch between the actual and expected sensory feedback can be used to make corrections to the movement trajectory (Kording et al., 2004; Shadmehr, 2004; Wolpert, 2007). A breakdown in any of these processes may contribute to the errors observed in the precision of the force production of individuals with MS. However, determining where

that breakdown may occur (i.e., motor planning, execution, or feedback stage) is inherently difficult due to the speed at which each of these processes occurs.

Within the past few decades, advances in neuroimaging techniques have allowed stage-like changes in neural oscillatory activity in the sensorimotor cortices to be identified, and these stage-like changes appear to correspond to the processes that occur during the planning and execution of movements. Electroencephalography (EEG) and magnetoencephalography (MEG) are currently the only brain imaging techniques with sufficient temporal resolution to assess these neural oscillations. Numerous EEG and MEG experiments have shown that prior to the onset of movement, cortical oscillatory activity across the sensorimotor cortices decreases in the beta frequency range (15-30 Hz) (Jurkiewicz et al., 2006; Cheyne et al., 2006, 2008; Gaetz et al., 2010; Muthukumaraswamy, 2010; Kurz et al., 2014; Wilson et al., 2014; Heinrichs-Graham & Wilson, 2015; Tzagarakis et al., 2015; Heinrichs-Graham et al., 2014, 2016). This decrease in the amount of power found in the beta band frequency, commonly termed beta desynchronization, is thought to reflect task-related changes in the firing rate of local populations of neurons, as they begin to prepare for the specific demands of the pending movement. The consensus is that this beta event-related desynchronization (ERD) is related to the formulation of the motor plan, because it occurs well before the onset of movement, occurs sooner for easier motor tasks, and because the amplitude of the response is influenced by the certainty of the movement pattern to be performed (Kaiser et al., 2001; Alegre et al., 2003; Tzagarakis et al., 2010). Additionally, upon completion of a movement, there is a robust beta frequency event-related synchronization, which is referred to as the post-movement beta rebound (PMBR) (Tzagarakis et al., 2010; Gaetz et al., 2010, 2011; Wilson et al., 2010, 2011). Traditionally, this PMBR was believed to represent the active inhibition of neuronal

networks after movement termination (Salmelin et al., 1995; Neuper & Pfurtscheller, 2001; Solis-Escalante et al., 2012) and/or afferent feedback to the motor cortices (Cassim et al., 2001; Houdayer et al., 2006; Parkes et al., 2006). However, recent experimental work has shown that changes in the PMBR may reflect the certainty of the feedforward motor actions that were executed based on the internal model (Tan et al., 2016).

While the central role of beta neural oscillatory activity in motor performance is well appreciated, there has been limited effort to use this knowledge to more precisely characterize the motor deficits seen in individuals with MS. Therefore, the purpose of this study was 1) to determine if beta oscillatory activity is altered in individuals with MS compared to healthy controls when completing a knee extension target matching task, and 2) to identify if there is a relationship between beta oscillatory activity and the precision of the knee joint muscular force production.

Methods

Subjects

Fifteen individuals with relapsing-remitting or secondary progressive MS (Age = 57.07 ± 6.26 yrs.; Female = 11) and fifteen healthy age and sex matched individuals (Age = 55.13 ± 6.93 ; Female = 12) participated in this study. The individuals with MS had an average Kurtzke Expanded Disability Status Scale of 5.5 ± 0.7 , which indicated that on average they could walk independently for at least 100 m. At the time of data collection, none of the patients had a relapse or a change in medication for at least 3 months. All testing was done at the University of Nebraska Medical Center. The Institutional Review Board at the University of Nebraska Medical Center reviewed and

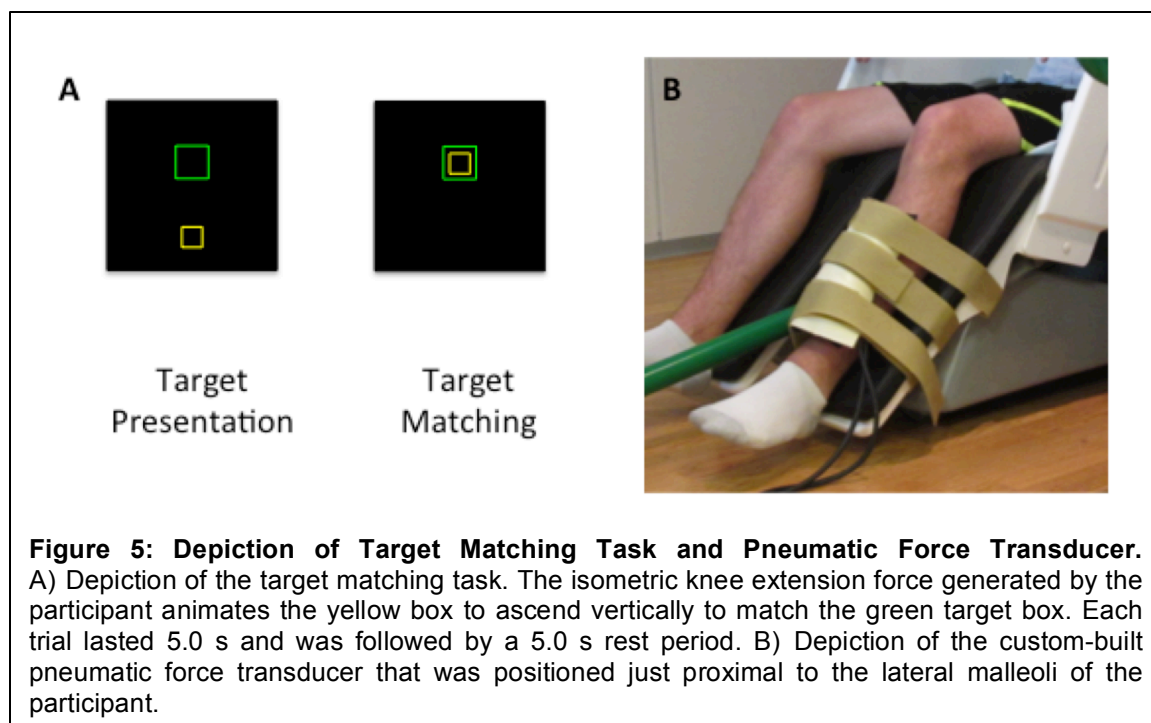
approved the protocol for this investigation. Additionally, all participants provided informed consent prior to participation in this study.

Experimental Paradigm

The participants were seated upright in a magnetically-silent chair. The experimental paradigm consisted of an isometric knee extension target matching task. The participants used their most affected leg (nondominant for the healthy comparison group) to match target forces that varied randomly between 5-30% of the participant's maximum isometric knee extension force. The target force was visually displayed as a box on a back-projection screen that was ~1 meter in front of the participant at eye level, and the force generated by the participant was shown as a smaller box (beneath the larger box) that moved vertically based on the isometric force generated (Figure 5A). Each participant performed 120 target matching trials. Each trial lasted 5.0 s and was followed by a 5.0 s rest period. A successful match occurred when the box representing the participant's isometric force was inside the target box for 0.3 s.

A custom-built magnetically-silent force transducer was used to measure the isometric knee extension forces generated by the participants (Figure 5B). This device consisted of a 20 x 10 cm airbladder that was inflated to 317 kPa, and fixed to the anterior portion of the lower leg just proximal to the lateral malleoli. A thermoplastic shell encased the outer portion of the airbladder and was secured to the chair with ridged strappings. Changes in the pressure of the airbag as the participant generated an isometric contraction were quantified by an air pressure sensor (Phidgets Inc., Calgary, Alberta, CA), and were subsequently converted into units of force. The force data was concurrently collected with the MEG data at 1 kHz. For each trial, the reaction time, amount of overshoot, average velocity to the target, time to initially reach the target, and the time to successfully match the target were computed offline. Separate t-tests at the

0.05 alpha level were used to determine if there were differences in the behavioral variables of the respective groups.



MEG Data Acquisition and Coregistration

All MEG recordings were conducted in a one-layer magnetically shielded room with active shielding engaged for advanced environmental noise compensation. During data acquisition, participants were monitored via real-time audio-video feeds from inside the shielded room. Neuromagnetic responses were acquired with a bandwidth of 0.1 – 330 Hz and were sampled continuously at 1 kHz using an Elekta Neuromag system (Helsinki, Finland) with 306 MEG sensors, including 204 planar gradiometers and 102 magnetometers. With the use of the MaxFilter software (Elekta), each MEG dataset was individually corrected for head motion during task performance and subjected to noise reduction using the signal space separation method with a temporal extension (Taulu & Simola, 2006).

Four coils were affixed to the head of each participant and were used for continuous head localization during the MEG experiment. Before the experiment, the location of these coils, three fiducial points, and the scalp surface were digitized to determine their three-dimensional position (Fastrak 3SF0002, Polhemus Navigator Sciences, Colchester, VT, USA). Once the participant was positioned for MEG recording, an electric current with a unique frequency label (e.g., 322 Hz) was fed to each of the four coils. This induced a measurable magnetic field and allowed each coil to be localized in reference to the sensors throughout the recording session. Since the coil locations were also known in head coordinates, all MEG measurements could be transformed into a common coordinate system. With this coordinate system (including the scalp surface points), each participant's MEG data was coregistered with structural T1-weighted MRI data using three external landmarks (i.e., fiducials) and the digitized scalp surface points prior to source space analyses. Structural MRI data were aligned parallel to the anterior and posterior commissures and transformed into the Talairach coordinate system (Talairach & Tournoux, 1998) using the volumetric subspace warping method implemented in BrainVoyager QX version 2.2 (Brain Innovations, The Netherlands).

MEG Pre-Processing

Artifact rejection was based on a fixed threshold method, supplemented with visual inspection. Two participants with MS and two controls were excluded from data analysis due to excessive MEG artifacts. The data analysis epochs were a total duration of 10.0 s (-3.0 to +7.0 s), with the onset of movement defined as time 0.0 s and the baseline defined as -2.0 to -1.2 s. Artifact-free epochs for each sensor were transformed into the time-frequency domain using complex demodulation (resolution: 2.0 Hz, 25 ms) and averaged over the respective trials to generate plots of the mean spectral density.

The data were then normalized by dividing the power value of each time-frequency bin by the mean power during the baseline period (-2.0 to -1.2 s). This normalization procedure allowed for the visual inspection of power changes that were present in sensor space.

Sensor Level Statistics

We determined the precise time-frequency bins of interest by conducting statistical analysis of the spectrograms corresponding to the gradiometers located near the sensorimotor cortices. Each data point in the spectrogram was initially evaluated using a mass univariate approach based on a general linear model. Briefly, we conducted unpaired t-tests on each data point to identify group differences, and the output spectrograms of t-values (one per sensor) were thresholded at $p < 0.05$. Next, the time-frequency bins that survived this threshold were clustered with temporally and/or spectrally neighboring bins that were also above the threshold, and a cluster value was derived by summing all of the t-values of all data points in the cluster. Nonparametric permutation testing was then used to derive a distribution of cluster values, and the significance level of the clusters was tested directly using this distribution. For each comparison, 10,000 permutations were computed to build a distribution of cluster values. Based on this analysis, the time-frequency windows that were significantly different between the two groups were identified for beamforming.

MEG Source Imaging & Virtual Sensor Extraction

A minimum variance vector beamforming algorithm was used to calculate the source power across the entire brain volume (van Veen et al., 1997; Gross et al., 2001). The single images were derived from the cross spectral densities of all combinations of the 204 MEG gradiometers within the time-frequency ranges of interest, and the solution

of the forward problem for each location on a grid specified by input voxel space. Following convention, the source power in these images were normalized per participant using a separately averaged pre-stimulus noise period of equal duration and bandwidth (Hillebrand et al., 2005). Thus, the normalized power per voxel was computed for the time-frequency ranges of interest over the entire brain volume per participant at 4.0 x 4.0 x 4.0 mm resolution. Each participant's functional images were transformed into a standardized space using the transform previously applied to the structural MRI volume (Talairach & Tournoux 1998). The MEG pre-processing and imaging was performed using the BESA software (BESA version 6.0), and MEG-MRI coregistration was performed using the BrainVoyager QX (Version 2.2) software.

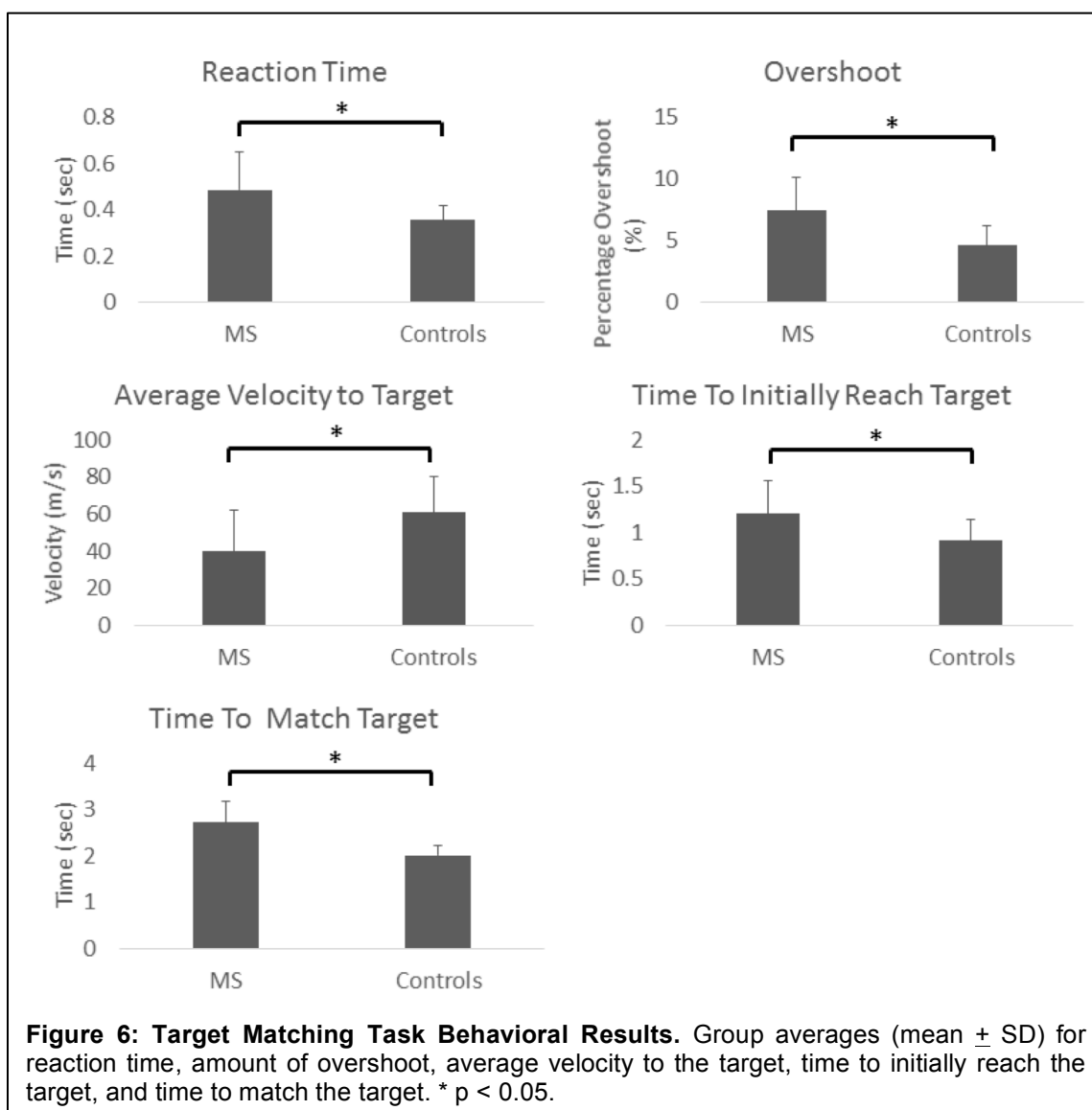
The individual beamformer images were averaged across all participants to identify the peak responses. We then extracted virtual sensors corresponding to the peak voxel of these responses. The virtual sensors were created by applying the sensor weighting matrix derived through the forward computation to the preprocessed signal vector, which resulted in a time series with the same temporal resolution as the original MEG recording (Heinrichs-Graham & Wilson, 2016). Once the virtual sensors were extracted, they were transformed into the time-frequency domain and the power, relative to baseline, was averaged across the frequency window of interest per unit time for each individual to derive the temporal evolution of the key oscillatory responses. Statistical analysis of these voxel time series was then performed using nonparametric permutation testing to determine differences between the two groups. Similar to our sensor space analysis, a cluster alpha of 0.05 was used, and 10,000 permutations were computed. Finally, we averaged the power across the time windows of interest for each individual to derive the strength of the event-related neural activity (see below). Pearson product

moment correlations were used to determine if there was a correlation between the strength of the event-related neural activity and the respective behavioral variables.

Results

Behavioral Analysis

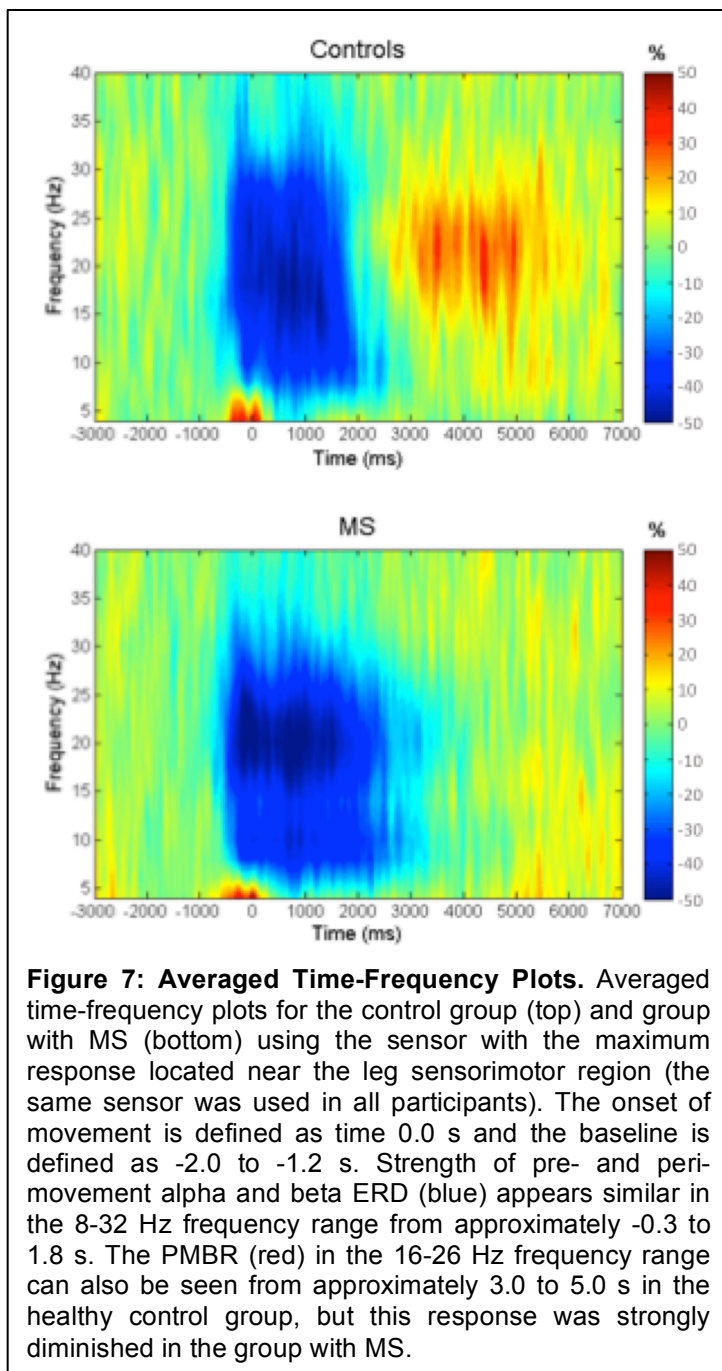
Significant differences were found between the two groups for all behavioral measures (Figure 6). Individuals with MS had a longer reaction time (MS = 0.49 ± 0.16 s, Controls = 0.36 ± 0.06 s, $p=0.01$), greater amount of overshoot (MS = 7.43 ± 2.69 %, Controls = 4.73 ± 1.56 %, $p=0.01$), lower average velocity to the target (MS = 40.0 ± 20.0 m/s, Controls = 60.0 ± 20.0 m/s, $p=0.01$), longer time to initially reach the target (MS = 1.2 ± 0.4 s, Controls = 0.9 ± 0.2 s, $p=0.01$), and longer time to match the target (MS = 2.8 ± 0.4 s, Controls = 2.0 ± 0.2 s, $p=0.01$).



Controls = 4.58 ± 1.59 %, $p < 0.01$), slower average velocity to the target (MS = 40.0 ± 19.7 m/s, Controls = 60.7 ± 22.0 m/s, $p = 0.02$), longer time to initially reach the target (MS = 1.20 ± 0.36 s, Controls = 0.91 ± 0.23 s, $p = 0.02$), and longer time to match the target (MS = 2.72 ± 0.47 s, Controls = 2.01 ± 0.23 s, $p < 0.01$). Altogether the results indicate that the precision of the isometric knee force production was reduced for the individuals with MS.

Sensor Level Analysis

Group averages of the peak sensor, located near the leg area of the sensorimotor cortices, are shown in Figure 7. Strong pre- and peri-movement beta (15-30 Hz) activity can be seen in the average data of both groups. Additionally, a strong PMBR can be seen in the healthy individuals, but this response appears to be absent in the individuals with MS. Based on our statistical analysis, we found no significant difference between the two groups for the pre- or peri-movement

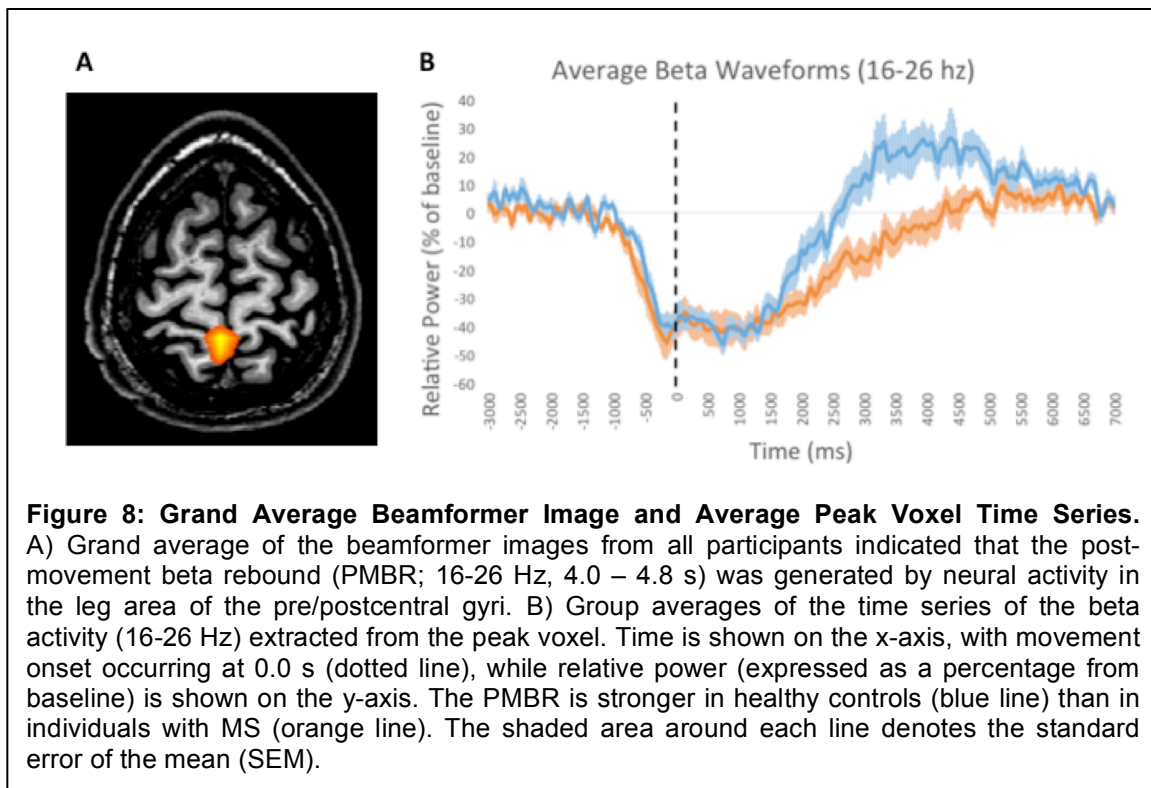


beta ERD ($p > 0.05$; corrected). However, a significant group difference ($p = 0.048$; corrected) was found for the PMBR ranging from 16-26 Hz from approximately 2.0 to 5.2 s. To image this neural response, we focused on the time window corresponding to the maximum PMBR (16-26 Hz; 4.0 to 4.8 s).

Beamformer and Peak Voxel Analysis

Beamformer images corresponding to the 4.0 to 4.8 s time window (16-26 Hz) were computed in each participant and averaged across both groups. The resulting data indicated that the PMBR originated near the leg area of the pre/postcentral gyri (Figure 8A). The peak voxel from this location was then extracted from this area and examined statistically. As expected, there continued to be no significant differences in the beta ERD between the two groups during the planning or execution period of the virtual sensor time course ($p > 0.05$; corrected). However, the strength of the PMBR was significantly weaker in the individuals with MS from 2.725 to 4.500 s ($p = 0.006$; corrected) and 4.575 to 5.025 s ($p = 0.047$; corrected) as shown in Figure 8B.

We also found moderate negative correlations between the strength of the PMBR and the time to successfully match the target ($r = -0.66$, $p < 0.01$), and reaction time ($r = -0.39$, $p = 0.05$). These correlations suggest that a stronger PMBR is related to improved performance on the target force matching task. No significant correlations were found between the strength of the PMBR and the amount of overshoot, average velocity to the target, or the time to initially reach the target (p 's > 0.05).



Discussion

The purpose of this study was to evaluate neural oscillatory activity in the sensorimotor cortices of individuals with MS and healthy individuals during a goal-directed knee extension task. Our primary finding was that individuals with MS exhibited a weaker PMBR in the precentral and postcentral gyri relative to healthy individuals. Our results also demonstrated that the precision of the isometric knee force production was reduced in individuals with MS, and that the strength of the PMBR was correlated with performance of the isometric knee force task.

Our MEG results showed no differences between individuals with MS and healthy in the pre- and peri-movement beta ERD. This finding was contrary to our prediction, as motor planning deficits have previously been reported in individuals with MS (Ternes et al., 2014). Prior EEG work also found that the latency and amplitude of

the beta ERD did not differ between healthy individuals and non-fatigued individuals with MS (classified by the Fatigue Severity Scale) (Leocani et al., 2001). However, this study did find increased beta ERD in fatigued individuals with MS compared to non-fatigued individuals and healthy individuals (Leocani et al., 2001). This may suggest that fatigue is related to motor planning deficits in individuals with MS. Given these somewhat conflicting reports, additional studies are warranted to further characterize the motor planning deficits seen in individuals with MS, and determine how they are associated with reported fatigue symptoms.

In our study, individuals with MS exhibited a weaker PMBR in the pre- and post-central gyri relative to healthy individuals. Similar findings were previously reported in an EEG study of self-paced movements of the hand in individuals with MS (Leocani et al., 2001). Together, these results provide mounting evidence that the PMBR response is disturbed in individuals with MS. Recent work indicates that the amplitude of the PMBR is related to the uncertainty in the feedforward estimations of the internal model (Tan et al., 2016). Since a stronger PMBR appears to be related to improved certainty of the internal model, we speculate that the internal model may be faulty in individuals with MS. Prior work appears to agree with this hypothesis. Using a multisensory model of sensory feedback control, Heenan et al. (2014) found that there appears to be a mismatch between the predicted and actual arm dynamics exhibited by individuals with MS during a reaching task. Furthermore, they suggest that the muscular control problems seen in individuals with MS may be due to an inability to adapt the internal estimate of movement duration to account for increases in the visual processing time. Taken together, this suggests that the internal model may become corrupt overtime due to demyelination in the cortical and spinal tracts that are necessary for relaying sensory feedback and properly updating the internal model.

Our behavioral results show that individuals with MS have impairments in the precision of the low extremity force production, which is consistent with our previous work (Davies et al., 2015; Arpin et al., 2016). Specifically, we found that individuals with MS had slower reaction times and a greater amount of overshoot of the presented targets. These impairments in behavioral performance may suggest motor planning deficits. However, no differences were seen in the pre-movement beta ERD, suggesting that motor planning was intact in these individuals. We propose that this apparent contradiction could be due to a number of factors. While motor planning may be intact, the demyelination of the cortical and spinal tracts may cause a delay in the signal from the cortex to the muscle (Conte et al., 2009). Alternatively, it is possible that the difference in reaction time is due to increased processing time required by individuals with MS to perform the appropriate sensorimotor transformations, as these fiber tracts may be damaged (Bonfiglio et al., 2006; Bonzano et al., 2009). This may be the best explanation, as there does not appear to be a difference in the latency of the pre-movement beta ERD, indicating the delayed reaction time is occurring prior to the formulation and execution of the motor plan. Finally, although the beta ERD appears similar, the motor plan is likely corrupt since the overshoot is substantially greater, indicating heightened errors in the motor output. This increase in the amount of overshoot may also indicate deficits in the ability to properly estimate the amount of force required to reach the target, further suggesting that the internal model may be corrupt in individuals with MS.

Lastly, we found correlations between the strength of the PMBR and the time to successfully match the target, as well as reaction time. These correlations suggest that a stronger PMBR is partially related to improved performance on the goal-directed knee force task. Moreover, these correlations imply that the strength of the PMBR is related to

the certainty of the internal model. Specifically, time to reach the target may indicate the integrity of the internal model by representing a measure of the ongoing comparisons that occur between the internal model and the current motor outcome (Kording et al., 2004; Shadmehr, 2004; Wolpert, 2007). Likewise, we speculate that the reaction time difference might represent a delay in the sensorimotor transformation, which could impact the ability to maintain and update the internal model.

Conclusion

Our results show that individuals with MS have impairments in the precision of the lower extremity force production, as well as reduced cortical oscillatory activity following movement termination. Since a stronger PMBR is related to improved certainty of the internal model, we speculate that the internal model is faulty in individuals with MS. Potentially, the internal model may become corrupt overtime due to the demyelination in the cortical and spinal tracts that are necessary for relaying sensory feedback and properly updating the internal model. We suggest that degradation in the PBMR deserves further attention because it may result in a novel biomarker that can be used to assess the efficacy of the current treatment protocols that are being used in MS.

CHAPTER 4: A REDUCED SOMATOSENSORY GATING RESPONSE IN INDIVIDUALS WITH MULTIPLE SCLEROSIS IS RELATED TO WALKING IMPAIRMENT

Introduction

Multiple sclerosis (MS) is an inflammatory autoimmune disease of the central nervous system (CNS) that results in demyelination of the axons in the brain and spinal cord. This demyelination reduces nerve conduction velocity, impairing the function of the CNS (White & Dressendorfer, 2004). While the symptoms vary widely between individuals, many experience mobility and balance impairments that limit their activities of daily living (Ellis & Motl, 2013). Approximately 50% of individuals with MS will require the use of a walking aid within 15 years of onset of the disease (Tremlett et al., 2006). Furthermore, approximately 70% of individuals with MS report gait dysfunction to be the most challenging aspect of the disease (LaRocca, 2011).

Historically, the clinical impression was that these mobility impairments were due to weaker muscles that fatigue at a faster rate (Armstrong et al., 1983; Chen et al., 1987; Ponichtera et al., 1992; Rice et al., 1992; Kent-Braun et al., 1997; Lambert et al., 2001). Although this is a likely factor, several prior studies have shown that sensory deficits, particularly loss of tactile sensation, are also related to impaired standing balance and walking performance in individuals with MS (Thoumie & Mevellec, 2002; Citaker et al., 2011). Despite this information, our understanding of the link between the sensory and motor systems is limited, and very few rehabilitation strategies have targeted the sensory impairments (Cattaneo et al., 2007; Gandolfi et al., 2015). Further interrogation of the sensory system, and its relation to motor function in individuals with MS, is needed to improve our understanding of the link between these two systems.

Sensory gating is a physiological process by which the central nervous system inhibits or suppresses redundant sensory information. Paired-pulse stimulation, which results in an attenuated neural response to an identical second stimulation when presented with a sufficiently short stimulus onset asynchrony, is commonly employed to assess sensory gating. This gating response is believed to serve as a protective mechanism, which prevents higher-order cortical centers from being flooded with unnecessary or redundant information (Boutros & Belger, 1999; Cheng et al., 2016). Historically, a number of sensory gating investigations have been used to establish that auditory gating deficits are associated with schizophrenia (Adler et al., 1982; Bramon et al., 2004; Cromwell et al., 2008). More recently, however, gating deficits have also been investigated in other neurologic populations (Jessen et al., 2001; Rosburg et al., 2008; Matsuzaki et al., 2014), as well as elderly individuals (Lenz et al., 2012). Additionally, despite the gating response occurring during the early stages of perceptual processing, it has been suggested that aberrant responses impact later cognitive processing and the formation of memories (Cheng et al., 2016). Moreover, a reduced somatosensory gating has been shown to be related to decreased tactile discrimination in older adults (Lenz, et al., 2012). Altogether these results imply that examination of sensory gating could provide unique information about the integrity of the sensory system.

The purpose of this investigation was to assess the integrity of the sensory system by quantifying sensory gating in individuals with MS. To this end, we applied paired-pulse electrical stimulation to the posterior tibial nerve while magnetoencephalography (MEG) was concurrently used to record neural responses. Additionally, we evaluated the spatiotemporal walking kinematics of these individuals to explore whether sensory gating may be related to the impaired mobility of individuals with MS.

Methods

Participants

Eleven individuals with relapsing-remitting or secondary progressive MS (Age = 56.1 ± 6 yrs.; Female = 9) and twelve healthy age and sex matched individuals (Age = 54.7 ± 7 ; Female = 9) participated in this study. The individuals with MS had an average Kurtzke Expanded Disability Status Scale of 5.5 ± 0.8 , which indicated that on average they could walk independently for at least 100 m. At the time of data collection, none of the patients had had a relapse or a change in medication for at least 3 months. All testing was done at the University of Nebraska Medical Center. The Institutional Review Board at the University of Nebraska Medical Center reviewed and approved the protocol for this investigation. Additionally, all participants provided informed consent prior to participation in this investigation.

Experimental Paradigm

The participants were seated with their eyes closed in a custom-made nonmagnetic chair with their head positioned within the MEG helmet-shaped sensor array. Unilateral electrical stimulation was applied to the right posterior tibial nerve using external cutaneous stimulators. For each participant, 120 paired-pulse trials were collected using an inter-stimulus interval of 500 ms and an inter-pair interval that randomly varied between 4.5 and 4.8 s. Each pulse was comprised of a 0.2 ms constant-current square wave that was increased in amplitude until there was a subtle flexion of the first phalange of the foot. Epochs were a total duration of 1.2 s, ranging from -0.2 to 1.0 s, with 0.0 s representing stimulation onset.

MEG Data Acquisition and Coregistration

All MEG recordings were conducted in a one-layer magnetically shielded room with active shielding engaged for advanced environmental noise compensation. During data acquisition, participants were monitored via real-time audio-video feeds from inside the shielded room. Neuromagnetic responses were acquired with a bandwidth of 0.1 – 330 Hz and were sampled continuously at 1 kHz using an Elekta Neuromag system (Helsinki, Finland) with 306 MEG sensors, including 204 planar gradiometers and 102 magnetometers. With the use of the MaxFilter software (Elekta), each MEG dataset was individually corrected for head motion during task performance and subjected to noise reduction using the signal space separation method with a temporal extension (Taulu & Simola, 2006).

Four coils were affixed to the head of the participant and were used for continuous head localization during the MEG experiment. Before the experiment, the location of these coils, three fiducial points, and the scalp surface were digitized to determine their three-dimensional position (Fastrak 3SF0002, Polhemus Navigator Sciences, Colchester, VT, USA). Once the participant was positioned for MEG recording, an electric current with a unique frequency label (e.g., 322 Hz) was fed to each of the four coils. This induced a measurable magnetic field and allowed each coil to be localized in reference to the sensors throughout the recording session. Since the coil locations were also known in head coordinates, all MEG measurements could be transformed into a common coordinate system. With this coordinate system (including the scalp surface points), each participant's MEG data was coregistered with structural T1-weighted MRI data using three external landmarks (i.e., fiducials) and the digitized scalp surface points prior to source space analyses. Structural MRI data were aligned parallel to the anterior and posterior commissures and transformed into the Talairach

coordinate system (Talairach & Tournoux, 1998) using the volumetric subspace warping method implemented in BrainVoyager QX version 2.2 (Brain Innovations, The Netherlands).

MEG Processing

Artifact rejection was based on a fixed threshold method, supplemented with visual inspection. Artifact-free epochs were time-domain averaged with respect to stimulus onset and then digitally filtered 0.1 to 120 Hz. The peak response to the first stimulation was evident at the sensor level and occurred approximately 80 ms after stimulation across all subjects. Thus a 40 ms window, centered over the peak of this response, was modeled as a regional current source using the subset of sensors that covered both magnetic flux extrema. The resulting regional sources were all located within the leg area of the primary somatosensory cortices and had an average goodness of fit of 0.70 ± 0.13 . We found the peak source amplitude of the response to the first stimulation (Peak 1) and the peak source amplitude of the response to the second stimulation (Peak 2). Using these peak amplitudes, we calculated the gating ratio by dividing Peak 2 by Peak 1. A gating ratio that is closer to 1 indicates a reduced gating response. Additionally, we calculated the latency to the peak of each of these responses.

Mobility Analysis

All participants were instructed to walk across a digital mat (GaitRITE, Sparta, NJ) at their preferred walking speeds. The mat digitized the locations of the feet, which were used to quantify the participant's walking velocity, cadence, step length and step width. Each participant completed two walking trials and the data from these two trials was averaged together.

Statistical Analysis

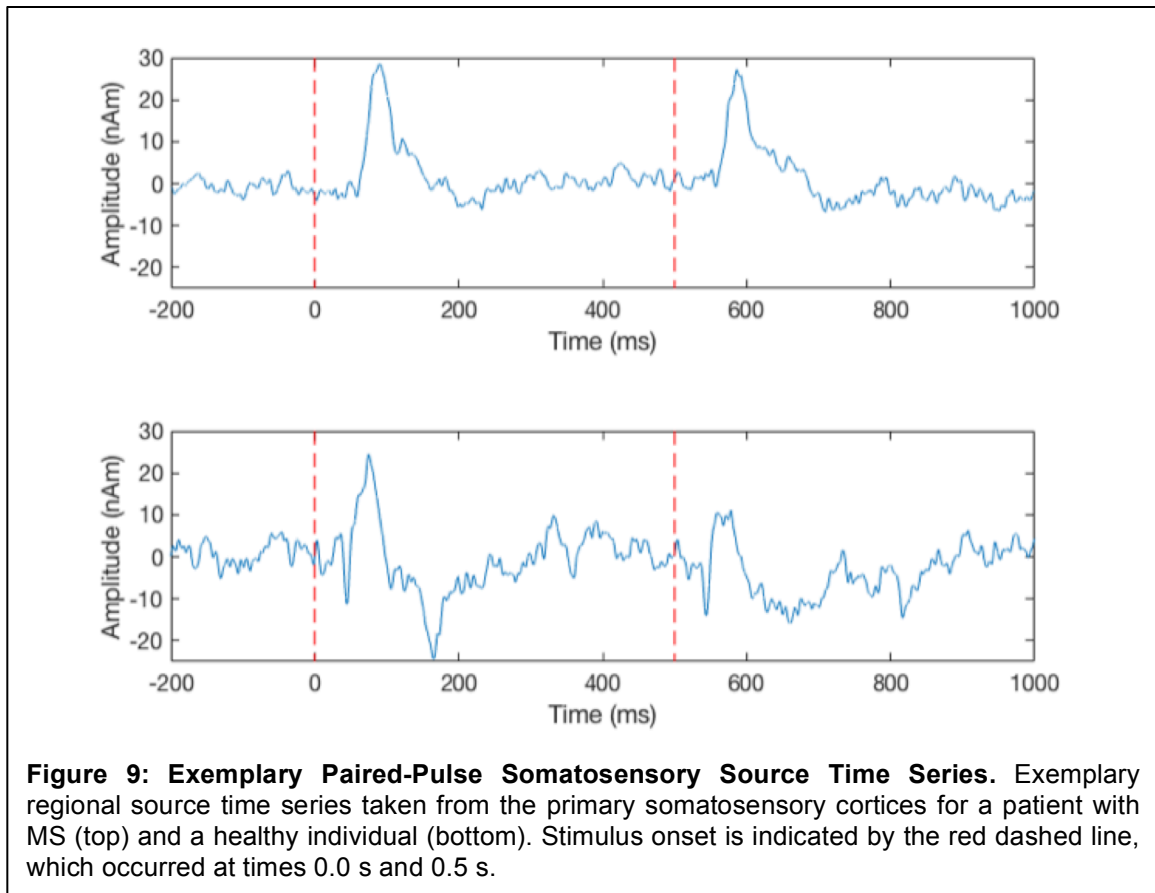
Shapiro-Wilk's test of normality was used to determine whether the data was normally distributed. Those data that failed the test were subsequently logarithmically transformed for all statistical testing. Separate mixed model (Group x Peak Number) ANOVAs with least-significant difference post hoc were used to examine the differences between patients with MS and healthy individuals for the latency and amplitude. Additionally, separate t-tests were used to determine if there were differences in the spatiotemporal kinematics, as well as the gating ratio, between the two groups. Spearman rho rank order correlations were subsequently performed between significant variables. All statistical analyses were performed in SPSS version 23 (IBM, Armonk, NY) at a 0.05 alpha level.

Results

MEG Analysis

Exemplary regional source time series from an individual with MS and a healthy individual are shown in Figure 9. Inspection of these time series clearly shows that the amplitude of the somatosensory response to the second stimulus is extenuated in the individual with MS compared with the healthy control. This response was typical of what was seen across all of the participants with MS.

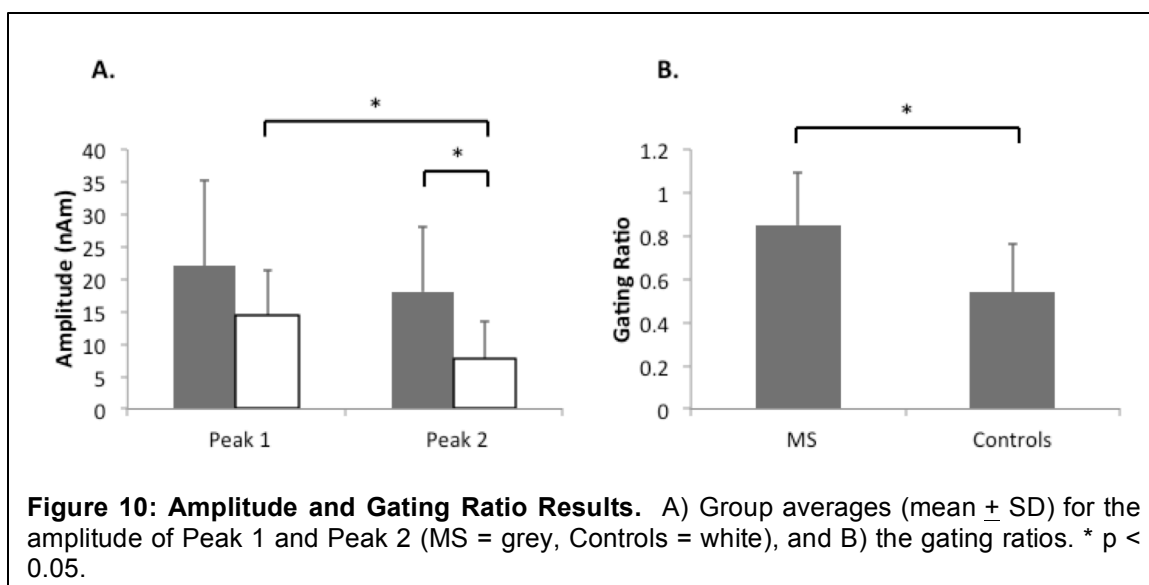
Analysis of the regional source time series revealed no significant group ($F(1,21) = 1.65$; $p = 0.21$) or peak ($F(1,21) = 1.13$; $p = 0.30$) main effect for latency, indicating that there were no differences in latencies between the two groups (MS = 83.41 ± 5.29 ms, Controls = 76.29 ± 5.06 ms) or between the response to the first and second stimuli (stimulus 1 = 80.35 ± 17.90 ms, stimulus 2 = 79.04 ± 17.61 ms).



There was a significant group main effect for amplitude ($F(1,21) = 8.97$; $p = 0.007$), with patients with MS having greater response amplitudes than healthy individuals (MS = 20.02 ± 2.70 nAm, Controls = 11.09 ± 2.58 nAm). There was also a significant peak main effect for amplitude ($F(1,21) = 19.806$; $p = 0.001$), indicating that the amplitude of Peak 1 was stronger than the amplitude of Peak 2 (Peak 1 = 18.06 ± 10.93 nAm, Peak 2 = 12.66 ± 9.55 nAm). There also was a significant peak x group interaction ($F(1,21) = 6.32$; $p = 0.02$). The post hoc analysis indicated that there was no significant difference between the two groups for the amplitude of Peak 1 (MS = 21.97 ± 13.29 nAm, Controls = 14.46 ± 6.99 nAm; $p = 0.10$). However, the amplitude of Peak 2 was significantly greater in patients with MS compared to healthy controls (Figure 10A; $p = 0.006$). There was also no significant difference between the amplitude of Peak 1 and

Peak 2 for the individuals with MS ($p = 0.44$). However, the healthy individuals had significantly reduced Peak 2 amplitudes relative to Peak 1 (Figure 10A; $p = 0.02$).

Our results also indicated that the individuals with MS had a significantly reduced somatosensory gating compared to healthy individuals ($p = 0.04$; Figure 10B). Taken together, this suggests that while there was not a significant difference in the latencies of the peak responses, the individuals with MS were not able to properly gate the response to the second stimulation.



Mobility Analyses

The spatiotemporal walking kinematics were significantly different between the two groups for all variables. At preferred walking speeds, individuals with MS had slower walking velocity (MS = 0.70 ± 0.27 m/s, Controls = 1.20 ± 0.16 m/s, $p < 0.01$), slower cadence (MS = 87.20 ± 16.44 steps/min, Controls = 107.73 ± 8.73 steps/min, $p < 0.01$), shorter step length (MS = 0.47 ± 0.11 m, Controls = 0.67 ± 0.07 m, $p < 0.01$), and wider step width (MS = 0.13 ± 0.06 m, Controls = 0.09 ± 0.03 m, $p < 0.01$).

There were moderate negative rank order correlations between the amplitude of Peak 2 and walking velocity ($r = -0.52$, $p < 0.01$) and step length ($r = -0.53$, $p < 0.01$).

These correlations implied that individuals that walked slower and used a shorter step length tended to have a larger amplitude for Peak 2. Additionally, we found a moderate positive correlation between the amplitude of Peak 2 and step width ($r = 0.47$, $p=0.01$). This correlation implies that individuals that used a wider step width tended to have a larger amplitude for Peak 2.

Moderate negative rank order correlations were also found between the gating ratio and walking velocity ($r = -0.37$, $p = 0.04$) and step length ($r = -0.39$, $p = 0.03$). Additionally, we found a moderate positive correlation between the gating ratio and step width ($r = 0.40$, $p = 0.03$). Altogether, these correlations imply that reduced somatosensory gating may be partially related to the mobility impairments seen in individuals with MS.

Discussion

This study examined the somatosensory gating in individuals with MS using applied paired-pulse electrical stimulation to the posterior tibial nerve. Our results demonstrated that individuals with MS showed a decreased somatosensory gating ability compared to healthy individuals. We also found differences in the spatiotemporal walking kinematics of individuals with MS compared to healthy individuals, which has been well documented in the MS literature (Benedetti et al., 1999; Kelleher et al., 2010; Arpin et al., 2016). Our results extend these observations by suggesting that sensory gating deficits are partially related to the poor mobility seen in these individuals.

Our results showed no differences in the latency of the amplitude of Peak 1 and Peak 2 between the two groups. This was unexpected, as it is well known that latent sensory responses often occur in individuals with MS due to demyelination (Trojaborg & Petersen, 1979). Potentially, this may be because we selected to use the response with

the largest amplitude, which occurred around 80 ms, rather than the early ~40 ms response sometimes reported in the literature (Nakanishi et al., 2014). We elected to use this later response because it showed the greatest change in amplitude and was the most reliable response. Furthermore, it has been suggested that somatosensory gating may be better assessed by later components of the somatosensory response (Thoma et al., 2007). Alternatively, it is possible that these sensory tracks remain intact and may not have been subjected to demyelination in the participants used for this experiment. However, we cannot support this conjecture because we did not have an assessment of the thalamocortical and spinal tract integrity. Further exploration of the relationship between the interplay between the integrity of the fiber tracks (i.e., diffusion tensor imaging) and the latency of the somatosensory cortical response is warranted.

No differences were seen between the two groups for the amplitude of Peak 1; however, the individuals with MS showed greater Peak 2 amplitudes compared to the healthy individuals. This difference resulted in reduced somatosensory gating for the individuals with MS compared to the healthy individuals. Currently, the exact mechanisms behind sensory gating are not fully understood; however, evidence suggests that gamma-aminobutyric acid (GABA) neurotransmitters modulate somatosensory gating (Huttunen et al., 2008). Damage to the inhibitory interneurons and dysregulation of GABA neurotransmitters have been reported in a histological study of individuals with progressive MS (Dutta et al., 2006). Therefore, the reduced somatosensory gating we observed may indicate that the activity of inhibitory intracortical circuits is altered in individuals with MS. Prior transcranial magnetic stimulation (TMS) studies appear to support this idea by showing that individuals with MS have reduced intracortical inhibition (Caramia et al., 2004; Liepert et al., 2005; Conte et al., 2009; Vucic et al., 2012). Furthermore, this notion is further supported by other

TMS studies that have identified that the impaired intracortical inhibition is related to EDSS scores (Conte et al., 2009; Vucic et al., 2012), and is apparent in individuals who are in the relapsing phase (Caramia et al., 2004).

Negative correlations were found between the amplitude of Peak 2 and walking velocity, as well as step length. This indicates that the individuals with an aberrant sensory gating response tended to walk slower and selected a shorter step length. Additionally, we found a positive correlation between the amplitude of Peak 2 and the step width, indicating that the individuals with an uncharacteristic sensory gating response also took wider steps, presumably to increase their base of support. Taken together, these results may suggest that reduced intracortical inhibition is partially related to the altered walking performance of individuals with MS. This notion is supported by prior work that has found that lower GABA concentrations in the sensorimotor cortex are related to reduced motor performance in individuals with secondary progressive MS (Cawley et al., 2015). In addition, several other studies have shown that the sensory deficits, particularly loss of tactile sensation and proprioception, are related to impaired standing balance and walking performance in individuals with MS (Thoumie & Mevellec, 2002; Citaker et al., 2011). Together this evidence suggests that the motor impairments present in individuals with MS are partially related to the neural computations associated with processing sensory information.

Conclusion

Our results show that individuals with MS have a reduced somatosensory gating response. This suggests that the inhibitory intracortical circuits may be altered in these individuals. Additionally, the altered spatiotemporal gait kinematics seen in the individuals with MS were related to the extent of the somatosensory gating. This suggests that the motor performance impairments seen in individuals with MS are

related to sensory processing deficits. We suggest that future investigations and clinical treatment protocols aimed at improving motor performance in these individuals place greater attention on improving these sensory processing deficits.

CHAPTER 5: REDUCED MOVEMENT-RELATED SOMATOSENSORY GATING IN INDIVIDUALS WITH MULTIPLE SCLEROSIS MAY INDICATE IMPAIRED SENSORIMOTOR INTEGRATION

Introduction

Multiple sclerosis (MS) is a demyelinating disease that impacts the function of the central nervous system, and often results in impaired muscular performance. Previously, we have shown that individuals with MS have greater errors when attempting to control the precision of the lower extremity force production (Davies et al., 2015; Arpin et al., 2016). While these results are insightful, the neurophysiological abnormalities that may be responsible for the reduced muscular force control remain unknown.

It is well established that the integration of sensory and motor information is essential to the performance of precise movements. However, previous work shows that individuals with MS often display sensory impairments (Rae-Grant et al., 1999). These sensory impairments could impact the motor performance of individuals with MS. For example, several studies have shown that sensory deficits, particularly loss of tactile sensation, are related to impaired standing balance and walking performance in individuals with MS (Thoumie & Mevellec, 2002; Citaker et al., 2011). Despite this information, our understanding of the interaction between the sensory and motor systems is limited, and few attempts have been made to target sensory impairments in the current rehabilitation strategies (Cattaneo et al., 2007; Gandolfi et al., 2015). Further interrogation of the sensory system, and its relation to motor function in individuals with MS, is needed to improve our understanding of the link between these two systems.

One way of probing the relationship between the sensory and motor systems is to assess the attenuation of neural responses to somatosensory stimulation during

movement. Numerous studies have demonstrated that somatosensory input to the cerebral cortex is attenuated (or gated) during and before voluntary movement, and during passive movements (Kristeva-Feige et al., 1996; Shimazu et al., 1999; Murase et al., 2000; Staines et al., 2000; Asanuma et al., 2003; Wasaka et al., 2003, 2005; Macerollo et al., 2016). Presumably this phenomenon represents how the central nervous system filters out irrelevant afferent information in order to efficiently process the most relevant stimuli (Rushton et al., 1981; Cohen & Starr, 1987; Saradjian, 2015). Additionally, several studies have suggested that movement-related sensory gating may be useful for investigating sensorimotor integration in healthy and clinical populations (Kristeva-Feige et al., 1996; Shimazu et al., 1999; Murase et al., 2000; Asanuma et al., 2003; Nakata et al., 2011).

This sensory attenuation phenomenon can originate from two main mechanisms. Sensory gating can occur through inhibitory interactions between the given sensory afferent signals and the afferent feedback from the muscles, joint, and skin caused by the movement itself. This mechanism is referred to as centripetal gating or peripheral gating, and can be thought of as a sensory competition between the afferent signals (Jones et al., 1989; Wasaka et al., 2003; Saradjian, 2015). Alternatively, sensory gating can occur through interactions between the given sensory afferent signals and the efferent signals induced by the motor command. This mechanism is referred to as centrifugal gating or central gating (Jones et al., 1989; Wasaka et al., 2003; Saradjian, 2015). Centripetal gating is thought to occur at the peripheral level as well as in the spinal cord and brain, while centrifugal gating might occur mainly in the cortex and subcortical structures (Wasaka et al., 2003). Furthermore, gating that occurs before the onset of movement must be the result of centrifugal gating, while gating that occurs during passive movement must be the result of centripetal gating (Jones et al., 1989).

However, gating during active movement may be due to a combination of both centrifugal and centripetal gating.

The purpose of this study was to assess movement-related somatosensory gating in individuals with and without MS. To this end, we applied single-pulse electrical stimulation to the posterior tibial nerve, both at rest and during movement, while magnetoencephalography (MEG) was concurrently used to record neural responses. Additionally, we evaluated the amount of variability or error in the motor output during a separate ankle control task to assess the motor performance of these individuals. Finally we explored whether movement-related somatosensory gating was related to motor performance.

Methods

Participants

Eleven individuals with relapsing-remitting or secondary progressive MS (Age = 57.0 ± 7 yrs.; Female = 9) and twelve healthy age and sex matched controls (Age = 54.3 ± 7 ; Female = 11) participated in this study. The individuals with MS had an average Kurtzke Expanded Disability Status Scale of 5.4 ± 0.8 . At the time of data collection none of the patients had had a relapse or a change in medication for at least 3 months. All testing was done at the University of Nebraska Medical Center. The Institutional Review Board at the University of Nebraska Medical Center reviewed and approved the protocol for this investigation. Additionally, all participants provided informed consent prior to participation in this investigation.

Experimental Paradigm

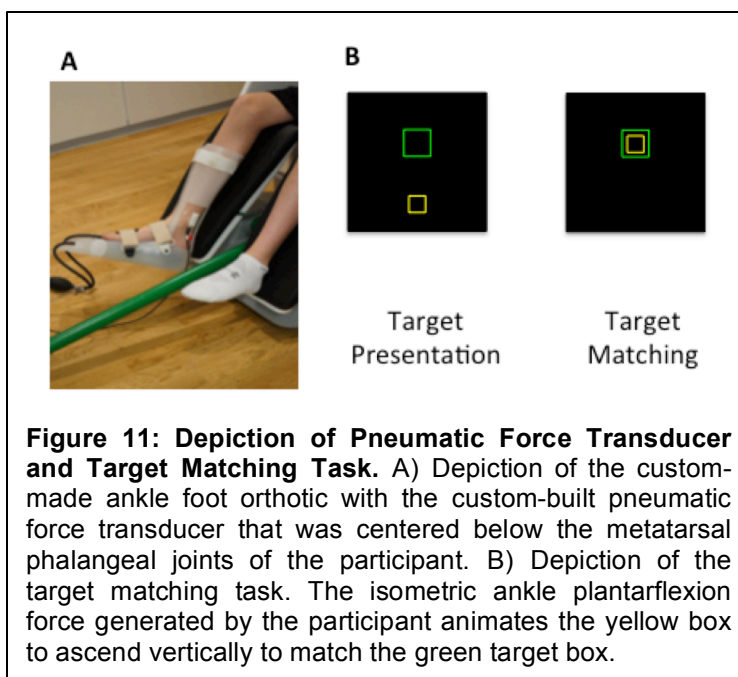
The participants were seated in a custom-made nonmagnetic chair with their head positioned within the MEG helmet-shaped sensor array. Unilateral electrical stimulation was applied to the right posterior tibial nerve using external cutaneous stimulators as the participant sat quietly focused on a fixation cross (passive condition), or performing an ankle force target matching task (active condition). During both the passive and active conditions, trials were collected using an inter-pair interval that randomly varied between 1.8 and 2.2 s. Each pulse was comprised of a 0.2 ms constant-current square wave that was increased in amplitude until there was a subtle flexion of the first phalange of the foot. Epochs were a total duration of 0.7 s, ranging from -0.2 to 0.5 s, with 0.0 s representing stimulation onset.

During the active condition participants were instructed to perform an isometric ankle plantarflexion target matching task. The participants used their right foot to match target forces that varied randomly between 5-30% of the participant's maximum isometric ankle plantarflexion force. The target force was visually displayed as a box on a back-projection screen that was ~1 meter in front of the participant at eye level, and the force generated by the participant was shown as a smaller box (beneath the larger box) that moved vertically based on the isometric force generated (Figure 11A). Each participant performed ~240 target matching trials. Each trial lasted 1.5 s and was followed by a 0.8 s rest period. The speed of the target matching task allowed us to increase the number of trials during which electrical stimulation occurred during movement.

A custom-built magnetically-silent force transducer was used to measure the isometric ankle plantarflexion forces generated by the participants. This device consisted of a 20 x 10 cm airbladder that was inflated to 317 kPa, and centered below the

metatarsal phalangeal joints. A custom-made ankle foot orthotic brace held the airbladder in place and secured it to the foot of the participant (Figure 11B). Changes in the pressure of the airbag as the participant generated an isometric contraction were quantified by an air pressure sensor (Phidgets Inc., Calgary, Alberta, CA), and were subsequently converted into units of force. The force data were sampled at 1 kHz and were used to identify movement onset in the MEG data.

Prior to the MEG recording, each participant performed an isometric ankle joint control task while seated within the MEG room, similar to the target matching task. The task was designed to measure the participant's control of their ankle joint musculature, and



consisted of two submaximal steady-state isometric contractions at 20% of their maximum voluntary force. Each steady-state contraction was performed for 30 seconds. The coefficient of variation ($CV = [\text{Standard Deviation of Force}/\text{Mean Force}] \times 100$) was used to assess the amount of variability present in the middle 15 seconds of the steady-state force. A lower CV value was an indication of greater motor control of the joint steady-state force (Christou & Tracy, 2006). These two trials were then averaged together for all data measures.

MEG Data Acquisition and Coregistration

All MEG recordings were conducted in a one-layer magnetically shielded room with active shielding engaged for advanced environmental noise compensation. During data acquisition, participants were monitored via real-time audio-video feeds from inside the shielded room. Neuromagnetic responses were acquired with a bandwidth of 0.1 – 330 Hz and were sampled continuously at 1 kHz using an Elekta Neuromag system (Helsinki, Finland) with 306 MEG sensors, including 204 planar gradiometers and 102 magnetometers. With the use of the MaxFilter software (Elekta), each MEG dataset was individually corrected for head motion during task performance and subjected to noise reduction using the signal space separation method with a temporal extension (Taulu & Simola, 2006).

Four coils were affixed to the head of the participant and were used for continuous head localization during the MEG experiment. Before the experiment, the location of these coils, three fiducial points, and the scalp surface were digitized to determine their three-dimensional position (Fastrak 3SF0002, Polhemus Navigator Sciences, Colchester, VT, USA). Once the participant was positioned for MEG recording, an electric current with a unique frequency label (e.g., 322 Hz) was fed to each of the four coils. This induced a measurable magnetic field and allowed each coil to be localized in reference to the sensors throughout the recording session. Since the coil locations were also known in head coordinates, all MEG measurements could be transformed into a common coordinate system. With this coordinate system (including the scalp surface points), each participant's MEG data was coregistered with structural T1-weighted MRI data using three external landmarks (i.e., fiducials) and the digitized scalp surface points prior to source space analyses. Structural MRI data were aligned parallel to the anterior and posterior commissures and transformed into the Talairach

coordinate system (Talairach & Tournoux, 1998) using the volumetric subspace warping method implemented in BrainVoyager QX version 2.2 (Brain Innovations, The Netherlands).

MEG Processing

Artifact rejection was based on a fixed threshold method, supplemented with visual inspection. Artifact-free epochs were time-domain averaged with respect to stimulus onset and then digitally filtered 0.1 to 120 Hz. The peak response to the electrical stimulation occurred approximately 70 ms after stimulation across all subjects, for both conditions. Thus a 40 ms window, centered over the peak of this response, was modeled as a regional current source using the subset of sensors that covered both magnetic flux extrema. The resulting regional sources were all located within the leg area of the primary somatosensory cortices and had an average goodness of fit of 0.82 ± 0.11 . We found the peak source amplitude of the response during both the passive and active conditions. Additionally, we calculated the latency to the peak of each of these responses.

Statistical Analysis

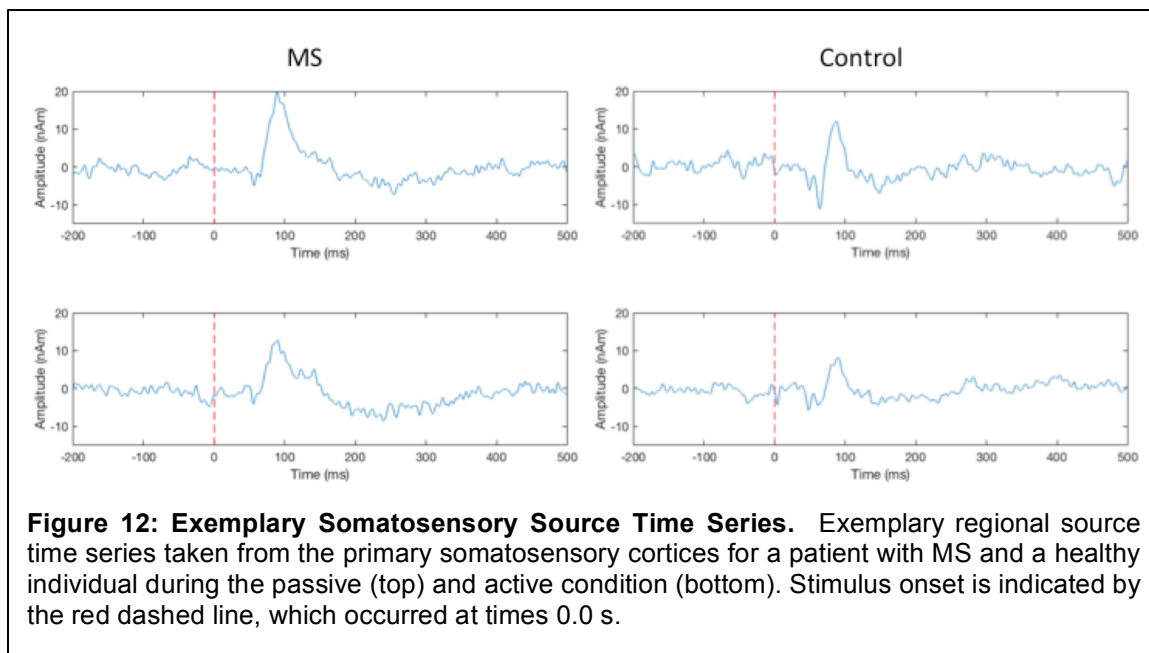
Shapiro-Wilk's test of normality was used to determine whether the data was normally distributed. Those data that failed the test were subsequently logarithmically transformed for all statistical testing. Separate mixed model (Group x Condition) ANOVAs with least-significant difference post hoc were used to examine the differences between patients with MS and healthy individuals for the latency and amplitude. Additionally, an independent samples t-test was used to determine if there were differences between the two groups in the CV for the ankle joint control task. Spearman rho rank order correlations were subsequently performed between the CV and the

respective sensory response data to assess the relationship between the sensory and motor systems. All statistical analyses were performed in SPSS version 23 (IBM, Armonk, NY) at a 0.05 alpha level.

Results

MEG Analysis

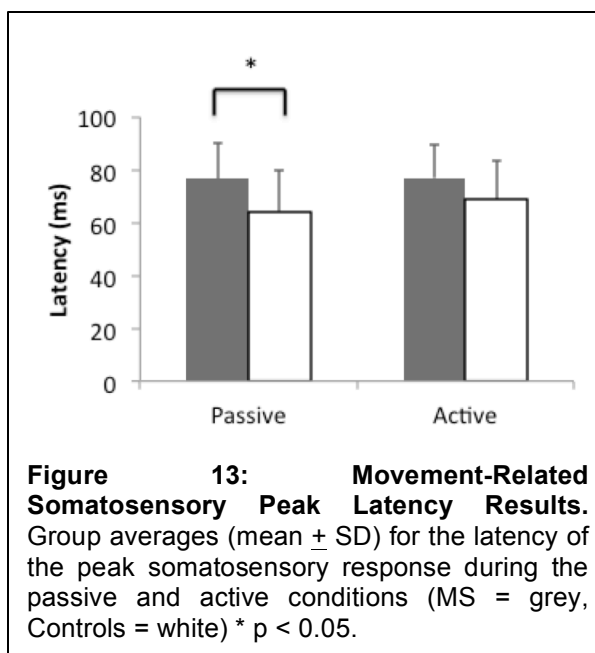
Exemplary regional source time series from an individual with MS and a healthy individual are shown in Figure 12. Inspection of these time series clearly shows that the amplitude of the somatosensory response during the active condition is extenuated in the individual with MS compared with the healthy control. This response was typical of what was seen across all of the participants with MS.



Analysis of the regional source time series revealed no significant group main effect for latency ($F(1,21) = 3.05$; $p = 0.09$). However, we did find a significant condition main effect for latency ($F(1,21) = 8.65$; $p = 0.008$), with the active condition having longer latencies than the passive condition (Passive = 70.13 ± 15.52 ms, Active = $72.65 \pm$

14.10 ms). There was also a significant condition x group interaction ($F(1,21) = 6.26$; $p = 0.02$). The post hoc tests indicated that there was a significant difference in latency between the two groups during the passive condition (MS = 76.55 ± 13.40 ms, Controls = 64.25 ± 15.48 ms; $p = 0.05$; Figure 13). However, no significant difference in latency was found between the two groups during the active condition (MS = 76.91 ± 12.45 ms, Controls = 68.75 ± 14.91 ms; $p = 0.17$). Additionally, no significant differences were found between the active and passive conditions for the individuals with MS ($p = 0.94$) or the healthy individuals ($p = 0.48$).

Additionally, we found no significant group main effect for amplitude ($F(1,21) = 0.81$; $p = 0.38$). However, we did find a significant condition main effect for amplitude ($F(1,21) = 14.67$; $p = 0.001$), with the active condition having lower amplitudes than the passive condition (Passive = 15.05 ± 7.93 nAm, Active = 10.52 ± 8.91 nAm). There was also a

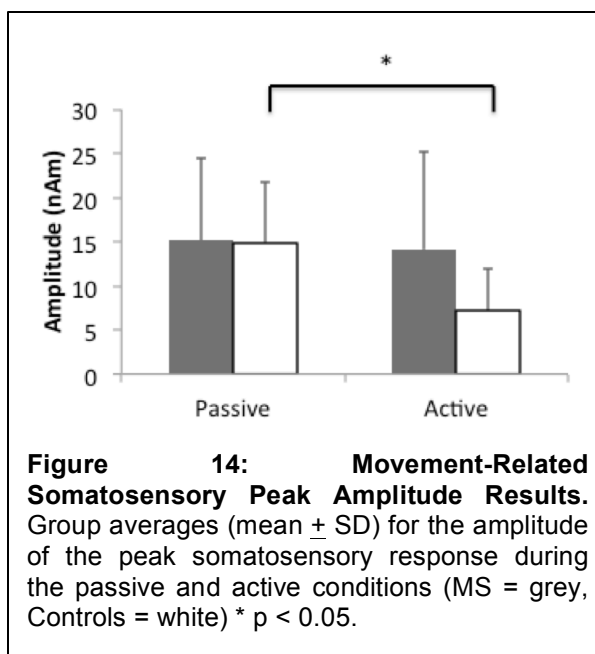


significant condition x group interaction ($F(1,21) = 4.94$; $p = 0.04$). The post hoc tests indicated that there was no significant difference in amplitude between the two groups during the passive condition (MS = 15.19 ± 9.26 nAm, Controls = 14.91 ± 6.90 nAm; $p = 0.93$), however the difference between the two groups during the active condition was trending (MS = 14.13 ± 11.12 nAm, Controls = 7.22 ± 4.63 nAm; $p = 0.06$). Additionally, no significant differences were found between the active and passive conditions for the individuals with MS ($p = 0.81$), however significant differences were found for the healthy

individuals ($p = 0.004$; Figure 14). This suggests that the ability to gate the somatosensory response during movement was diminished in the individuals with MS.

Ankle Joint Control and Correlation Analyses

No significant difference was found between the two groups for the CV (MS = 2.42 ± 1.22 , Controls = 2.05 ± 1.10 , $p = 0.23$). However, a moderate positive correlation was found between the CV and the active amplitude ($r = 0.51$, $p = 0.01$). No significant correlations were found between the CV and the passive amplitude, or the latencies ($p > 0.05$). This suggests that an inability to gate the somatosensory response during movement may be partially related to the poor motor performance of individuals with MS.



Discussion

This study examined movement-related somatosensory gating in individuals with and without MS using single-pulse electrical stimulation to the posterior tibial nerve, and the relation of movement-related somatosensory gating to motor performance. Our results demonstrated sensory gating during movement in the healthy individuals; however, individuals with MS were unable to properly gate the somatosensory response during movement. Our results also suggest that the inability to modulate the somatosensory response during movement is partially related to the poor motor control seen in individuals with MS.

Our results showed that the active condition had longer latencies to the peak amplitude than the passive condition when the groups were combined. Additionally we found that the individuals with MS had longer latencies to the peak amplitude than the healthy controls during the passive condition. This is in agreement with prior work showing increased sensory response latencies in individuals with MS, likely due to demyelination (Trojaborg & Petersen, 1979). However, no difference in latency to the peak amplitude was found between the two groups during the active condition. This may in part be because we selected to use the response with the largest amplitude, which occurred around 70 ms, rather than the early ~40 ms response sometimes reported in the literature (Nakanishi et al., 2014). Alternatively, it may be because the sensory attenuation seen during movement also alters the response latency. The increased latency in the active condition when combined across groups may support this theory, however, no differences were seen between the active and passive conditions when the groups were separated.

No differences were seen in peak amplitude between the active and passive conditions for the individuals with MS; however, the healthy individuals showed reduced peak amplitudes during the active condition compared to the passive condition. This indicates that the individuals with MS were unable to properly gate the sensory response during movement. Potentially, this could indicate a sensorimotor integration deficit in individuals with MS (Kristeva-Feige et al., 1996; Shimazu et al., 1999; Murase et al., 2000; Asanuma et al., 2003; Nakata et al., 2011). In agreement with this, impaired sensorimotor integration has previously been reported in circuits involving both the corpus callosum and the brain stem in individuals with MS (Cabib et al., 2015). Additionally, neuroimaging studies have demonstrated extensive involvement of the thalamus and basal ganglia in individuals with MS (Calabrese et al., 2010b; Minagar et

al., 2013). Furthermore, direct recordings from the thalamus suggest that the thalamus is involved in movement-related sensory gating (Costa et al., 2008). It has also been suggested that the basal ganglia is involved in gating sensory influences onto motor areas of the brain (Menon et al., 1998). Taken together this suggests that the deficits we have found in movement-related somatosensory gating in individuals with MS could potentially be a result of damage to the thalamus and basal ganglia. However, MS results in damage to the entire CNS, making it difficult to identify where the breakdown in movement-related sensory gating may occur.

An alternative explanation may be that the activity of inhibitory intracortical circuits is altered in individuals with MS, resulting in failure to properly gate somatosensory responses during movement. Damage to the inhibitory interneurons and dysregulation of gamma-aminobutyric acid (GABA) neurotransmitters have previously been reported in a histological study of individuals with progressive MS (Dutta et al., 2006). Prior transcranial magnetic stimulation (TMS) studies also appear to support this idea by showing that individuals with MS have reduced intracortical inhibition (Caramia et al., 2004; Liepert et al., 2005; Conte et al., 2009; Vucic et al., 2012). Additionally, this notion is further supported by other TMS studies that have identified that the impaired intracortical inhibition is related to EDSS scores (Conte et al., 2009; Vucic et al., 2012), and is apparent in individuals who are in the relapsing phase (Caramia et al., 2004).

In this study we used an isometric contraction during the active condition. In doing so, we accounted for the fact that somatosensory response amplitudes can be influenced by the position of the limb (Staines et al., 1996). Additionally, the isometric task eliminated afferent information due to changes in joint position and muscle length; however, the cutaneous receptors still provide afferent information related to the amount of pressure exerted on the force transducer. As a result, we were not able to determine

whether the individuals with MS displayed deficits specifically in centrifugal or centripetal gating. We believe it is likely that both centrifugal and centripetal gating are impacted by the demyelination due to the disease, however, future studies may potentially be able to investigate this by assessing sensory gating during motor preparation or during passive movement.

Finally, our results showed no difference between the two groups for the CV during the ankle control task. This was surprising as we have previously shown differences in control of the ankle joint musculature between individuals with MS and healthy individuals (Arpin et al., 2016). We did, however, find a moderate positive correlation between the CV during the ankle control task and the peak amplitude of the somatosensory response during the active condition. This indicates that greater movement-related sensory gating occurs in individuals who have better motor performance. This is in agreement with previous work, which indicated that greater gating is related to faster reaction times (Seki & Fetz, 2012) and greater task difficulty (Rushton et al., 1981). Taken together, this suggests that movement-related sensory gating is important to motor performance, although the exact nature of this relationship remains unclear.

Conclusion

Our results show that individuals with MS have a reduced movement-related somatosensory gating response. Additionally, we found that the control of the ankle joint musculature was related to the extent of the movement-related somatosensory gating. These results indicate that movement-related somatosensory gating is impaired in individuals with MS, and potentially represents impaired sensorimotor integration. We suggest that future investigations and clinical treatment protocols aimed at improving

motor performance in these individuals place greater attention on improving these sensory processing deficits.

DISCUSSION

Main Outcomes

The main purpose of this dissertation was to assess the behavioral and neurophysiological deficits present in individuals with MS in order to increase our understanding of their motor impairments. More specifically, this dissertation used a combination of behavioral measures and high-density MEG recording to quantify the motor outcomes and cortical activity of individuals with MS and a group of healthy age matched controls. The outcomes of this series of studies will provide insight into the motor control impairments present in individuals with MS, and may be useful in developing novel treatment strategies designed to improve the motor control of these individuals.

In the first study, we behaviorally quantified the precision of the steady-state isometric control of the ankle plantarflexor musculature of individuals with MS, and evaluated whether the precision of the ankle joint was related to mobility impairment. Our main hypothesis was that the individuals with MS would have a greater amount of error in the steady-state isometric ankle plantarflexion task, indicating motor control impairments. Additionally, we hypothesized that the precision of the ankle plantarflexors would be related to the spatiotemporal gait kinematics. Our results supported our hypotheses, indicating that the individuals with MS had a greater amount of variability in the precision of the isometric ankle torques. Furthermore, this greater amount of variability in isometric ankle torque was related to decreased walking performance. These results further fuel the impression that a reduction in control of the ankle joint musculature may be a key factor in the mobility and balance impairments seen in individuals with MS. Additionally, we speculated that the increased variability in ankle plantarflexion performance was due to damage within the CNS which impacted the

cortical activation associated with planning motor actions (Leocani et al., 2001, 2005). This hypothesis was the foundation for the second study in this dissertation.

To assess the hypothesis developed based on the results of the first study, the second study explored the motor planning and execution stages of movement during a goal directed target matching task performed with the knee joint. Our specific hypothesis here was that the beta ERD would be reduced both prior to, and at movement onset in individuals with MS. Interestingly, our results did not support this hypothesis, as no differences were found between groups in the beta activity during the planning and execution stages of movement. This appears to suggest that motor planning remains intact in individuals with MS. However, our behavioral results showed that the final motor output was faulty. This suggested that the motor plan was likely corrupt, since the behavioral measures indicated greater errors in motor performance. Additionally, we did find that individuals with MS had a weaker PMBR in the precentral and postcentral gyri relative to healthy controls. This finding was of interest because prior work has suggested that the strength of the PMBR may indicate the certainty of the internal model (Tan et al., 2016). We also found that the behavioral performance of individuals with MS was aberrant, and related to the strength of the post-movement beta rebound. Based on these results, we speculate that the internal model is faulty in individuals with MS. Potentially, the internal model may become corrupt overtime due to the demyelination in the cortical and spinal tracts that are necessary for relaying sensory feedback and properly updating the internal model.

The third study of this dissertation assessed the integrity of the sensory system, since proper sensory feedback is essential to accurately updating the internal model. To assess the sensory system we examined the somatosensory gating response using a paired-pulse tibial nerve stimulation paradigm. Our hypothesis was that individuals with

MS would display an aberrant somatosensory gating response, which would be related to their motor performance. Indeed, we found that the amplitude of the response to the second stimulation was properly reduced in healthy individuals, but not in the individuals with MS. This resulted in reduced somatosensory gating for the individuals with MS, suggesting the inhibitory intracortical circuits may be altered in these individuals. Additionally, we found that the altered spatiotemporal gait kinematics seen in the individuals with MS were related to the extent of the somatosensory gating. This suggests that the motor performance impairments seen in individuals with MS are related to sensory processing deficits.

Building on the results of the previous study, we examined how the sensorimotor cortex responded to single-pulse tibial nerve stimulation both at rest and during movement. This provided an indication of how the sensory system was performing during movement, and how sensory feedback impacts motor control in individuals with MS. In this final study, we hypothesized that individuals with MS would display aberrant sensorimotor cortical activity in response to tibial nerve stimulation both at rest and during movement, and that this aberrant cortical activity would be related to behavioral measures of motor control. We found no differences in the amplitude of the response between the two groups during the passive condition. However, we did find a trend toward a larger amplitude response in the individuals with MS compared to the healthy individuals during the active condition. We also found that the healthy individuals displayed the typical reduction in amplitude of the neural response to somatosensory stimulation during movement, while the individuals with MS were unable to properly suppress this neural response. Finally, we found that the control of the ankle joint musculature was related to the extent of the movement-related somatosensory gating. These results indicated that movement-related somatosensory gating is impaired in

individuals with MS, and potentially represents impaired sensorimotor integration. All together, the results of this dissertation provide evidence that the impaired motor control of individuals with MS may be due to a faulty internal model, which has become corrupt due to demyelination, and cannot be properly updated due to impaired sensory processing.

Limitations

There were several limitations to the experiments conducted in this dissertation. First, each of these investigations was limited by a small sample size. The small sample sizes make it difficult to know whether these results can be extrapolated to characterize MS in general, or are simply representative of the individuals who participated in these experiments. Additionally, it should be noted that the individuals with MS who participated in these studies were classified as having either relapsing-remitting or secondary progressive MS. Due to the small sample sizes we were unable to focus on one specific type of MS, and are therefore unable to comment on how our results may differ based on type of MS.

Another limitation was that these studies all used isometric target matching tasks to assess muscular control, however, the isometric tasks used in these studies likely do not approximate the ankle or knee control required during gait. These tasks were used, in part, because of the limitations inherent in brain imaging. However, using a more dynamic force matching task may have also been possible, and may have provided a better approximation of the muscular control required during gait. Future investigations with larger sample sizes should confirm the results of these studies, and explore whether differences exist among the types of MS. Furthermore, experimental methods that include more dynamic force matching tasks should be explored, as these may provide a closer approximation of the muscular control required during gait.

Future Direction

The results of this work supports the theory that the PMBR is related to improved certainty of the internal model, and suggests that the internal model is faulty in individuals with MS. Therefore, future studies should further investigate degradation in the PBMR, as it may result in a novel biomarker that can be used to assess the efficacy of the current treatment protocols that are being used in MS. Additionally, the results of the two studies that assessed the neural responses to somatosensory stimulation indicated that individuals with MS have sensory processing deficits. However, few attempts have been made to target sensory impairments in the current rehabilitation strategies (Cattaneo et al., 2007; Gandolfi et al., 2015). Therefore, further investigations of the efficacy of rehabilitation strategies targeting sensory impairments in comparison to standard rehabilitation strategies are needed. These types of studies have attempted to improve sensory deficits through exercises that challenge the deficient sensory system, such as balance training with the eyes closed to challenge the vestibular and proprioceptive systems, or balance training on unstable surfaces to challenge the visual and vestibular systems. Future studies should also aim to develop novel methods of targeting the sensory systems, such as through biofeedback devices, in order to find optimal methods of improving these sensory deficits.

Conclusion

This dissertation explored the behavioral and neurophysiological deficits present in individuals with MS in order to increase our understanding of their motor impairments. The results of these studies added to the body of literature identifying impairments in the gait, and lower extremity muscular control, of individuals with MS. More importantly, this work provides new insight into these motor control deficits, suggesting they may be the result of a corrupt internal model. Furthermore, these results suggest that these

impairments may arise from sensory processing deficits, which prevent individuals with MS from properly updating their internal model. These outcomes provide new insight into the motor control impairments present in individuals with MS, and may be useful in developing novel treatment strategies designed to improve the motor control of these individuals.

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