Submaximal Isometric Force Steadiness in People with Multiple Sclerosis Under Single and Dual Task Conditions

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SUBMAXIMAL ISOMETRIC FORCE STEADINESS IN PEOPLE WITH MULTIPLE SCLEROSIS UNDER SINGLE AND DUAL TASK CONDITIONS

by

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A Dissertation submitted to the Faculty of the Graduate School,
Marquette University,
in Partial Fulfillment of the Requirements for
the Degree of Doctor of Philosophy

Milwaukee, Wisconsin

May 2020

ABSTRACT
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Marquette University, 2020

Activities of daily living require steady, non-fatiguing, isometric muscular contractions to maintain postural control and stabilize body segments to facilitate interaction with the environment. Furthermore, typical activities often require simultaneous performance of cognitive and motor tasks. This may challenge people with multiple sclerosis, a chronic neurodegenerative disease of the central nervous system associated with motor and cognitive impairments. Despite functional relevance, isometric force steadiness in both the upper and lower extremities of this population has not been explored. Additionally, dual task experiments in multiple sclerosis have primarily used gait, a dynamic activity, as the motor task. Thus, the purpose of this dissertation was to examine isometric force steadiness performed under single and dual task conditions in people with multiple sclerosis. It was hypothesized that people with multiple sclerosis would be less steady and have greater dual task costs of cognitive-motor tasks.

Study one measured steadiness of the ankle dorsiflexors and elbow flexors across a range of low to moderate force targets during a single task condition. Absolute force fluctuation at each target was measured and relative fluctuation was calculated using the coefficient of variation. In the elbow flexors, people with multiple sclerosis were less steady than controls only at very low forces and were less steady at nearly all force targets in the ankle. However, magnitudes of upper and lower extremity force fluctuation did not correlate within either sample.

Study two determined dual task effects of simultaneous performance of a steady ankle dorsiflexion contraction and a cognitive task involving working memory and processing speed. Both controls and people with multiple sclerosis experienced negative dual task effects on motor and cognitive performances. Although those with multiple sclerosis did not perform as well as controls for all tasks, there was no difference in motor effects.

This dissertation shows that 1.) isometric steadiness is impaired in the upper and lower extremities of people with multiple sclerosis at very low forces under single task conditions, 2.) people with multiple sclerosis experience cognitive-motor interference when dual tasking, and 3.) the relative dual task motor effects are nonetheless comparable to what is experienced by healthy controls.

ACKNOWLEDGEMENTS

Sheri L. Bunyan

I am thankful for my primary advisor, Dr. Alex Ng, who continually modeled enthusiasm in pursuing scientific curiosity, and to my committee, Dr. Julie Bobholz, Dr. Sandra Hunter, and Dr. Kristy Nielson, for helping me not only navigate this venture, but also for inspiring high standards for future work. I am especially appreciative of the faculty, staff, and students in the Exercise Science Department at Marquette University who provided encouragement, shared resources, and created a positive environment where graduate students were both challenged and valued.

This dissertation would not have reached fruition without the research participants who generously shared their time, especially those with multiple sclerosis who also shared wisdom, and personal narratives of perseverance. Your inspirational stories have motivated me to push forward and appreciate life's challenges and blessings.

The most meaningful experience I have gained from this endeavor is receiving limitless love, support, and encouragement from my husband, John, and my sons, Michael and Jack. I am certain that my boys cannot remember a time when I was not only pursuing this degree, but also working full-time. You embraced the grind with me and our family has grown closer because of it. My futile efforts to construct a perfect message expressing love and gratitude have shown me that words will never convey even a fraction of what is in my head and heart. You've filled my life with laughter, jokes, and dance parties in the kitchen, and I am grateful to be a part of our family.

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LIST OF ABBREVIATIONS

η_{p2}	Partial eta squared
9HPT	9-hole peg test
25(OH)D	25-hydroxy vitamin D
25FWT	25-foot walk test
BBS	Berg balance scale
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CESD	Centers for Epidemiology Depression Scale
CIS	Clinically isolated syndrome
CMI	Cognitive motor interference
CNS	Central nervous system
CSF	Cerebrospinal fluid
CPG	Clinical practice guideline
CV	Coefficient of variation
DS	Disease steps
DTE	Dual task effect
GWAS	Genome wide association study
EBV	Epstein-Barr virus
EDSS	Expanded disability status scale
EMG	Electromyography
FAMS	Functional assessment of multiple sclerosis
FDI	First dorsal interosseous
FGA	Functional gait assessment
fMRI	Functional magnetic resonance imaging
HLA	Human leukocyte antigen
Hz	Hertz

IgG	Immunoglobulin G
IM	Infectious mononucleosis
IU	International units
kg	Kilogram
L	Liter
M1	Primary motor cortex
m	Meter
MEP	Motor evoked potential
MFIS	Modified fatigue impact scale
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSFC	Multiple sclerosis functional composite
MVIC	Maximal voluntary isometric contraction
NARCOMS	North American Research Committee on Multiple Sclerosis
Nm	Newton meter
nmol	Nanomole
OR	Odds ratio
PASAT	Paced auditory serial addition test
PASAT-3	Paced auditory serial addition test stimuli; presented every 3 seconds
PASAT-4	Paced auditory serial addition test stimuli; presented every 4 seconds
PDDS	Patient-determined disease steps
PPMS	Primary progressive multiple sclerosis
QOL	Quality of life
RIS	Radiologically isolated syndrome
RR	Relative risk
RPMS	Relapsing progressive multiple sclerosis
RRMS	Relapsing remitting multiple sclerosis

s	Seconds
SD	Standard deviation
SE	Standard error of the mean
SNP	Single nucleotide polymorphism
SPMS	Secondary progressive multiple sclerosis
TMS	Transcranial magnetic stimulation
TUG	Timed Up-and-Go
TUGc	Timed Up-and-Go cognitive
UVB	Ultraviolet B

CHAPTER 1. LITERATURE REVIEW AND DISSERTATION AIMS

The experiments in this dissertation seek to understand the relation between upper and lower extremity force steadiness in a population with multiple sclerosis (MS) and to determine the effect of simultaneous performance of cognitive and motor tasks in the same population. Thus, this literature review provides an overview of the disease and a summary of literature pertaining to force steadiness and dual cognitive-motor task performance in adults with MS.

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic, progressive, autoimmune disorder in which a process of inflammation and demyelination progressively damages axons and myelin-producing oligodendrocytes of the central nervous system (Compston & Coles, 2008; Noseworthy, Lucchinetti, Rodriguez, & Weinshenker, 2000; Sospedra & Martin, 2016). The first section of this review addresses recent evidence pertaining to the epidemiology, etiology, clinical presentation, and diagnostic criteria for MS. Recent changes in estimation of incidence and prevalence will be covered, as well as updates to diagnostic criteria.

Epidemiology

Although the lifetime risk of acquiring MS is low in the general population (Compston & Coles, 2008), it is one of the most common acquired neurodegenerative

diseases affecting relatively young people with an average age at onset between 29 and 30 years of age (Global Burden of Diseases 2016 Multiple Sclerosis Collaborators, 2019; World Health Organization, 2008).

Prevalence, the number of cases of a disease at a particular point in time (Portney & Watkins, 2015), is widely reported in the MS literature. Recent studies report that MS affects up to 420,000 people in the United States (Dilokthornsakul et al., 2016) and between 2.1 and 2.3 million people worldwide (Browne et al., 2014), with the greatest prevalence in developed nations located in northern latitudes (World Health Organization, 2008). Additionally, there is a sex difference in prevalence (Dilokthornsakul et al., 2016; Global Burden of Diseases 2016 Multiple Sclerosis Collaborators, 2019; Wallin et al., 2019) with 2.8 females affected for each male (Wallin et al., 2019).

Although commonly reported, prevalence is not easily determined. It is typically estimated using statistical modeling and accessible data including large datasets from insurance providers or health systems. Estimates of prevalence can be influenced by sampling errors in which the dataset selected for analysis does not do not does not accurately reflect the target population. A prevalence algorithm developed by Wallin and colleagues (2019) analyzed datasets in the United States using databases from private insurance companies, Medicare, Medicaid programs, and the Veterans Administration. They concluded that the prevalence of MS in the United States is vastly underestimated. Their model estimates that approximately 720,000 people are currently living with the disease as opposed to cited statistics that report half as many cases.

Incidence, the number of new cases of disease observed during a particular period of time (Portney & Watkins, 2015), is more difficult to ascertain than prevalence. Incidence provides a better estimate of risk of acquiring a condition than prevalence. Currently, there is a worldwide trend of increasing incidence of MS (Alonso & Hernán, 2008; Browne et al., 2014; Multiple Sclerosis International Federation, 2013). However, a lack of global standardization in reporting cases of MS necessitates caution in the interpretation of specific point estimates (Evans et al., 2013; Global Burden of Diseases 2016 Multiple Sclerosis Collaborators, 2019). In developing nations, the incidence of MS is increasing in conjunction with improved access to advanced diagnostic technology, particularly magnetic resonance imaging (MRI) equipment (Multiple Sclerosis International Federation, 2013). Therefore, it is possible that the increase in global incidence of MS may be related to an improved capability to detect new cases rather than an increase in global risk of acquiring the disease.

Consistent with worldwide data, evidence suggests that the incidence of MS is increasing in North America (Alonso & Hernán, 2008; Evans et al., 2013; Wallin et al., 2019). Wallin and colleagues (2019) gathered epidemiologic data about individuals in the United States who received health care benefits through major insurers, the Veterans Administration, Medicare, or Medicaid programs. Data were collected between 2008 and 2010 and, although incidence was not directly calculated and reported, an increase in cumulative prevalence was noted across this relatively brief period. Regardless of inconsistencies in determining prevalence and incidence, it is clear that many are affected by MS and that this population is growing.

Etiology

It is generally accepted that the etiology of multiple sclerosis is complex and involves interaction of genetic and environmental factors. A single, salient target for interventions aimed at preventing MS has not been identified. However, a robust body of literature links MS to several risk factors including genetic predisposition (Ascherio & Munger, 2008; Canto & Oksenberg, 2018; Cotsapas, Mitrovic, & Hafler, 2018; Dyment, Ebers, & Dessa Sadovnick, 2004; Hafler et al., 2007; Levin et al., 2005; Olsson, Barcellos, & Alfredsson, 2016), exposure to Epstein-Barr virus (EBV) (Ascherio, 2013; Ascherio, Munger, & Lünemann, 2012; Correale & Gaitán, 2015; Olsson et al., 2016), Vitamin D insufficiency (Ascherio, 2013; Ascherio et al., 2012; Correale & Gaitán, 2015; Munger, Levin, Hollis, Howard, & Ascherio, 2006; Olsson et al., 2016), childhood obesity (Ascherio, 2013; Huppke et al., 2019; Mokry et al., 2016; Munger et al., 2013; Munger, Chitnis, & Ascherio, 2009; Olsson et al., 2016; Wesnes et al., 2014), and cigarette smoking (Ascherio & Munger, 2008; Olsson et al., 2016). A recent meta-analysis examined over 400 primary research articles exploring the relation between environmental risk factors and the development of MS. Three key risk factors were identified; Immunoglobulin G (IgG) production detected in serum with exposure to EBV antigen, history of infectious mononucleosis (IM), and cigarette smoking (Bellou, Evangelou, Ioannidis, & Tzoulaki, 2015).

Genetic Factors

Genetic contributions to the development of MS have largely been supported by two types of studies, those in which the rates of MS diagnoses were observed in families and those that explored genetic variants people with MS. While the absolute lifetime risk of developing MS in the general worldwide population is approximately 0.01% (Compston & Coles, 2008), relative risk (RR) increases in individuals who have a family members with the disease (Canto & Oksenberg, 2018; Compston & Coles, 2008; Dyment et al., 2004). However, estimates of risk vary among published reports.

The extent to which familial association increases MS risk appears linked to the degree of genetic information shared between the at-risk individual and family member with MS. Willer and colleagues (2003) examined Canadian twins and discovered that monozygotic siblings had a greater rate of MS concordance (25.3%), than dizygotic siblings (5.4%). These findings are consistent with others who also examined concordance in twins from other parts of the world (Ebers et al., 1986; Hansen et al., 2005; Kuusisto et al., 2008; Mumford et al., 1994; Ristori et al., 2006; Robertson et al., 1996). Sadovnik and colleagues (1988) were among the first to report increased risk in first, second, and third degree relatives of people with MS, a finding supported by subsequent investigators who also found that risk decreases as genetic links weaken between the at-risk individual and family member with MS (Compston & Coles, 2008; Dyment et al., 2004).

A commonly cited work by Compston & Coles (2008) reports lifetime risk of acquiring MS based upon pooled data from patient surveys. This report provides point estimates and 95% confidence intervals for various levels of genetic sharing.

Monozygotic twins who share identical genetic information at birth have the greatest risk of recurrence with a point estimate of approximately 30%. When the amount of shared genetic information is halved, risk drops to about 24% for a child with two affected parents and to 14% for a child with a single affected parent. Risk further decreases in second and third degree relatives to approximately 1% (Compston & Coles, 2008).

When considering familial risk, it is important to note that the highest rate of association identified in this literature review was 25% for monozygotic twins (Willer et al., 2003). This suggests that even though risk is substantially higher than that of the general population, it is still unlikely that one twin will acquire MS when the other is affected. To better understand susceptibility, one must be mindful that diagnostic criteria for MS require that a patient experience an episode of neurologic impairment (Thompson, Banwell, et al., 2018). It is possible that an individual could experience neural degeneration associated with MS without reaching the threshold of impairment required for diagnosis. This notion is supported by a recent abstract presented at a 2016 conference hosted by the European Committee for Treatment and Research in Multiple Sclerosis. Researchers reported preliminary findings of a German study examining monozygotic twins in which one twin had MS and the other did not. MRI findings of 44 twins who were not diagnosed with MS were analyzed. Twenty-nine of these asymptomatic twins had CNS lesions consistent with MS (Gerdes et al., 2016). Therefore, it can be argued that risk estimates with an outcome of clinically-definite MS may not adequately capture the risk of experiencing asymptomatic neurodegeneration in family members that could precede MS.

The other primary methods of examining genetic contributions to MS include genome-wide association study (GWAS) and linkage analysis. GWAS involves scanning the complete genomes of people with and without a condition of interest and comparing them to identify single nucleotide polymorphisms (SNPs) associated with the disease (NIH National Human Genome Research Institute, 2016). GWAS is a relatively new approach to genetic research predicated upon the ability to sequence the entire genome. Linkage analysis, a technique used to identify genetic markers associated with disease in family members at risk for specific conditions (NIH National Cancer Institute, 2019), was commonly used to examine genetic contributions to MS prior to availability of GWAS.

Recent reviews report that both linkage analysis and GWAS have discovered a strong association between MS and variations of genes encoding human leucocyte antigen (HLC) located on the short arm of chromosome 6 (Figure 1.1) (Canto & Oksenberg, 2018; Dobson & Giovannoni, 2019; Dyment et al., 2004; Hollenbach & Oksenberg, 2015; Lin, Charlesworth, van der Mei, & Taylor, 2012; Sawcer, Franklin, & Ban, 2014). The *HLA-DR15* gene has been confirmed to be of particular importance. The odds of developing MS are three times greater in those with *HLA-DR15* variants that in those without (Canto & Oksenberg, 2018; Dobson & Giovannoni, 2019; Lin et al., 2012). HLA genes code for major histocompatibility complex (MHC) proteins that play a role in adaptive immunity by presenting intracellular proteins to the surface of a cell to signal that trigger immune responses directed at the antigen-presenting cell (Kindt, Osborne, & Goldsby, 2006).

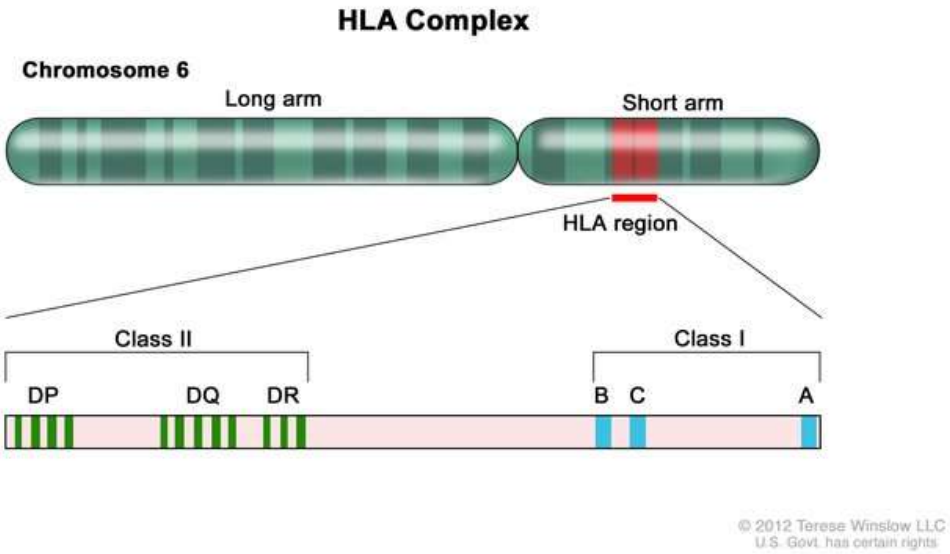


Figure 1.1: Human Leukocyte Antigen Complex: Abnormalities in HLA, located on the short arm of chromosome 6 is strongly associated with development of MS. Figure by Terese Winslow. Reprinted with permission of Terese Winslow.

Although the genes that encode antigen-presenting molecules in the HLA complex account for the greatest portion of genetic susceptibility, this region is not the only portion of the genome associated with MS. Over 200 genetic variants outside this region have been implicated in increased susceptibility (Canto & Oksenberg, 2018; Dyment et al., 2004) and the relation between genetic variants and risk is nonlinear (Dyment et al., 2004; Hollenbach & Oksenberg, 2015) highlighting the need to consider environment factors and the way they interact with multiple genes associated with MS.

Epstein-Barr Virus

Exposure to EBV is an important environmental risk factor for development of MS. EBV is a type of herpes virus, transmitted via saliva (Ascherio et al., 2012), with

double-stranded DNA that is experienced by up to 90% of the population (Ascherio, 2013; Ascherio et al., 2001; Goodin, 2015; Sven Haahr & Höllsberg, 2006). When contracted early in life, EBV infection presents as a typical childhood illness. However, if acquired in adolescence, symptoms become more profound and can result in more serious conditions including mononucleosis (Ascherio, 2013; Ascherio et al., 2001; Sven Haahr & Höllsberg, 2006).

Despite strong link between EBV exposure and MS, causal mechanisms have not been determined with certainty (Ascherio, 2013; Ascherio et al., 2001; Sven Haahr & Höllsberg, 2006; Levin et al., 2005) and researchers cannot confidently explain why only a fraction of those infected with EBV develop MS (Ascherio, 2013; Sven Haahr & Höllsberg, 2006). One hypothesis is that initial EBV infection affects both B-cells and T-cells, components of the adaptive immune system (Ascherio, 2013). B-cells function in part circulating in the blood, sampling for antigen known as foreign or potentially infectious, and ultimately releasing antibodies to help eradicate the threat. One subtype of T-cell, also called cytotoxic or killer T-cells, function by binding to antigen expressed on an infected cell and destroying the cell by releasing proteins that weaken the cell membrane and elicit intracellular processes that ultimately result in apoptosis (Kindt et al., 2006). It is possible that initial EBV infection results in B-cells learning to respond to the virus. Subsequent infection activates these educated B-cells that subsequently provoke vigorous, persistent cytotoxic T-cell responses. This process is hypothesized to make B-cells more resistant to auto-regulatory signals (Ascherio, 2013; Ascherio et al., 2012). Another hypothesis suggests that EBV is located in MS lesions and directly

triggers immune responses. However, postmortem examinations of MS lesions have inconsistently reported the presence of EBV (Ascherio, 2013).

What is known is that EBV exposure, especially exposure that results in infectious mononucleosis (IM), increases risk of developing MS. Aschiero (2013) reported relative risk using a typical person, one infected with EBV but with no history of IM, as a reference (RR = 1.0). Aschiero reported a lower risk of developing MS in those who were negative for EBV infection (RR = 0.08) and higher in one with EBV and a history of IM (RR = 2.3). This agrees with the findings of a Danish study in which MS risk was compared between those who developed IM late in childhood following EBV infection and those infected with EBV who did not develop IM. They determined MS risk to be 2.8 times greater in those who experienced IM (S. Haahr, Koch-Henriksen, Møller-Larsen, Eriksen, & Andersen, 1995).

Vitamin D

Vitamin D appears to have protective, immunomodulatory effects against MS (Ascherio, 2013; Ascherio et al., 2012; Munger et al., 2006; Salzer et al., 2012; Sintzel, Rametta, & Reder, 2018) and individuals with inadequate intake or low serum levels of Vitamin D have a higher risk of acquiring the disease (Ascherio, 2013; Ascherio et al., 2012; Munger et al., 2006; Munger et al., 2004; Salzer et al., 2012). The specific mechanisms by which Vitamin D affects the immune system in MS are not fully understood. However, the association between Vitamin D and MS risk is important because Vitamin D insufficiency can be addressed with relative ease via supplementation.

Evidence links inadequate intake of Vitamin D to MS. Munger and colleagues (2004) assessed this link using data from two studies on health of registered nurses in the United States. They analyzed data from two large studies, the Nurses' Health Study and Nurses' Health Study II, in which 187,563 female nurses completed health questionnaires periodically between 1980 and 2000. The questionnaires inquired about diet and nutritional supplement use. As cases of MS became evident in the sample, researchers were able to assess the association between that phenomenon and Vitamin D intake. After adjusting for smoking, obesity, and latitude, it was determined that the relative risk of developing MS in those who supplemented at least 400 international units (IU)/day of Vitamin D was approximately 40% lower than females who did not use supplements (Munger et al., 2004). Even though these findings depended upon self-reported dietary intake, researchers supported validity by comparing the intake reports to reports of hip fractures and found an inverse relation between the two factors. This comparison is helpful as Vitamin D is related to bone health.

It is important that the findings of Munger (2004) are not overestimated. Vitamin D supplementation of 400 IU/day may have been augmented by exposure to direct sunlight. Although researchers did control for latitude with the understanding that people in northern latitudes do not receive as much sunlight as those at lower latitudes, they did not measure direct exposure to ultraviolet B radiation in sunlight. This is significant because approximately 10,000 IU is endogenously produced with twenty minutes of full body exposure (Ascherio, Munger, & Simon, 2010; Sintzel et al., 2018).

Studies have not only examined Vitamin D intake, but also serum Vitamin D concentrations, specifically 25-hydroxyvitamin D (25(OH)D). Many studies examine

25(OH)D concentration in people who have already been diagnosed with MS. A study by the United States Department of Defense collected serum samples and health records in more than 7 million male and female military personnel over a five-year period. Data including serum concentrations of 25(OH)D. During the observation period, 257 new cases of MS emerged. Each MS case was matched to two control cases and 25(OH)D concentrations were compared. The risk of developing MS was 50% lower in Caucasian males and females with 25(OH)D concentrations > 100 nmol/L than in people with concentrations < 75 nmol/L. Furthermore, Caucasians experienced a 41% decrease in MS risk for each 50 nmol/L increase in 25(OH)D. There was no significant association between these variables in African Americans who developed MS (Munger et al., 2006).

Even though identification and understanding of mechanisms are lacking, associations between Vitamin D and MS are compelling enough to result in a shift in conceptualizing Vitamin D as playing a role in more than bone health. In fact, the Endocrine Society released a clinical practice guideline (CPG) defining an adequate serum 25(OH)D concentration as $\geq$ 75 nmol/L (Holick et al., 2011), a value larger than the 50nmol/L concentration advocated by the Institute of Medicine that primarily considers skeletal benefits (Sintzel et al., 2018).

It is logical to study geographic prevalence of MS when considering that Vitamin D is synthesized in skin exposed to ultraviolet B (UVB) radiation from sunlight. Ample research has documented a higher prevalence of MS in latitudes further from the equator (Ascherio, 2013; Ascherio & Munger, 2008; Ascherio et al., 2012; Sintzel et al., 2018). However, the effect of latitude may be diminishing (Alonso & Hernán, 2008; Koch-Henriksen & Sorensen, 2011; Koch-Henriksen & Sørensen, 2010). Possible reasons

include increased ability to detect and report MS in developing nations near the equator, increased emphasis on sun protection in the United States, and an increasing incidence of EBV infection in southern regions of the United States where the virus previously had lower rates of infection than in the north (Sintzel et al., 2018).

Obesity

Obesity increases risk of developing MS (Ascherio, 2013; Huppke et al., 2019; Mokry et al., 2016; Munger et al., 2013; Munger et al., 2009; Munger et al., 2004; Olsson et al., 2016; Wesnes et al., 2014). Potential mechanisms are not fully understood, but it is suggested that bioavailability of Vitamin D is limited in people with obesity because it is sequestered in adipose tissue (Holick et al., 2011).

Data from the Nurses' Health Study found that 18 year-old females with body mass index (BMI) measures of ≥ 30 kg/m^2, defined by the Centers for Disease Control and Prevention (CDC) as obesity (Centers for Disease Control and Prevention, 2017), had a risk 2.25 times greater than females with BMIs between 18.5 and 20.9 kg/m^2 (Munger et al., 2009), classified as normal weight by the CDC (Centers for Disease Control and Prevention, 2017). This agrees with a Swedish study that found the risk of MS doubled in 20 year-old females with a BMI of > 27kg/m^2 (Hedström, Olsson, & Alfredsson, 2012) and a Norwegian study that discovered increased risk in obese males and females (Wesnes et al., 2014). Another study used a GWAS method to examine genetically determined BMI and found that an increase in actual BMI of a single standard deviation

above this value resulted in a 41% increase in MS (Mokry et al., 2016). These studies provide evidence that obesity in young adults increases risk of developing MS.

Recent investigations have explored the relation between obesity in childhood and development of MS later in life. A case control study in Denmark explored school health records that included BMI measures of more than 300,000 children. These data were cross-referenced with the Danish MS Registry, MS cases were identified, and MS risk was calculated with obesity as the risk factor. It was found that each single unit increase in BMI increased MS risk by 15-20%. Furthermore, female children with a BMIs at or above the 95th percentile had an MS risk between 60-90% higher than those at or below the 85th percentile (Munger et al., 2013). This agrees with findings of a German study that retrospectively examined BMI in children diagnosed with MS. They discovered that children with obesity not only had twice the risk of developing MS, but also responded poorly to initial pharmacological treatment (Huppke et al., 2019).

Tobacco Smoking

The final salient epidemiological consideration included in this review is tobacco smoking, a modifiable risk factor that is thought to exacerbate adverse genetic processes associated with MS (Lin et al., 2012; Thompson, Baranzini, Geurts, Hemmer, & Ciccarelli, 2018). Researchers studying large cohorts of Europeans and Americans have consistently found that risk of developing MS increases in smokers (Hedström, Bäärnhielm, Olsson, & Alfredsson, 2009; Hernán, Oleky, & Ascherio, 2001; Riise, Nortvedt, & Ascherio, 2003; Salzer et al., 2013; Sundström, Nyström, & Hallmans,

2008). Furthermore, MS risk also increases with exposure to secondhand smoke (Mikaeloff, Caridade, Tardieu, & Suissa, 2007). In those who have MS, smoking worsens prognosis and is associated with a more rapid progression of symptoms associated with neurodegeneration (Manouchehrinia et al., 2013; Ramanujam et al., 2015; Sundström & Nyström, 2008; Wingerchuk, 2012). It seems that these increased risks are attributable to smoking, not nicotine. Although a dearth of evidence exists, a Swedish study did not find an increased risk of developing MS in smokeless tobacco users (Hedström et al., 2009) .

Risk studies of smoking and MS reported odds ratios (OR) and risk ratios (RR) ranging between 1.10 (Hernán et al., 2001) and 2.40 (Salzer et al., 2013). Although these ratios are relatively low, it is important to note that these values were adjusted for potential confounding behaviors known to be associated with MS risk. For example, Munger (2009) found that females with obesity smoked at higher rates than females of normal BMI and Munger (2004) found that females who used Vitamin D supplements were less likely to smoke tobacco. Another consideration in appraising this literature is the methodology used to calculate risk. Most studies calculated risk using self-reported smoking history. A study measuring cotinine, a biomarker for exposure to tobacco smoke, in females recently diagnosed with MS reported an odds ratio of 3.1 (Sundström et al., 2008), a higher risk than what was calculated in studies using self-reports of tobacco smoking. It can be confidently stated that smoking increases MS risk regardless of the methods used to calculate risk and sample participants in these epidemiological studies.

Clinical Presentation of Multiple Sclerosis

MS is a progressive neurodegenerative disease that produces damage throughout the CNS. Because the sites and severity of autoimmune activity and neural degeneration vary among those with the disease, concomitant clinical presentations vary as well (Filippi et al., 2018; Thompson, Baranzini, et al., 2018). All neural tissue in the CNS is a potential target for autoimmune processes associated with MS. Therefore, clinical signs and symptoms vary between people with disease presentation depending upon the location and extent of neural damage. Variability of clinical presentation also exists within individuals with MS. It is common for signs and symptoms to change over both the course of a day and over the lifetime of a person with the disease. Symptoms of MS may include fatigue, somatosensory disturbance, visual impairment, weakness, incoordination, spasticity, general impairments of gait and balance, cognitive impairment, and autonomic dysfunction (Cameron & Nilsagard, 2018; Compston & Coles, 2008; Filippi et al., 2018; Noseworthy et al., 2000; Olek, 2005; Thompson, Baranzini, et al., 2018; Widener, 2007). The ensuing sections of this literature review describe MS phenotypes and the clinical presentations of on MS germane to the measures used in the experiments of this dissertation.

Multiple Sclerosis Phenotypes

An advisory committee convened by the United States' National MS Society defined clinical phenotypes of MS in 1996 to improve consistency in communication among health care providers and scientists. An international panel of experts introduced

four phenotypes based upon the clinical course of the disease: relapsing remitting (RRMS), primary progressive (PPMS), secondary progressive (SPMS), and relapsing progressive (RPMS). Two additional terms, benign MS and malignant MS, were included to describe disease severity. The panel acknowledged a lack of consensus on the best way to define RPMS (Lublin & Reingold, 1996). This terminology was subsequently embraced by the MS community and widely used in research and clinical practice. Recently, it was reexamined and new recommendations were made by the International Advisory Committee on Clinical Trials in Multiple Sclerosis (Lublin et al., 2014).

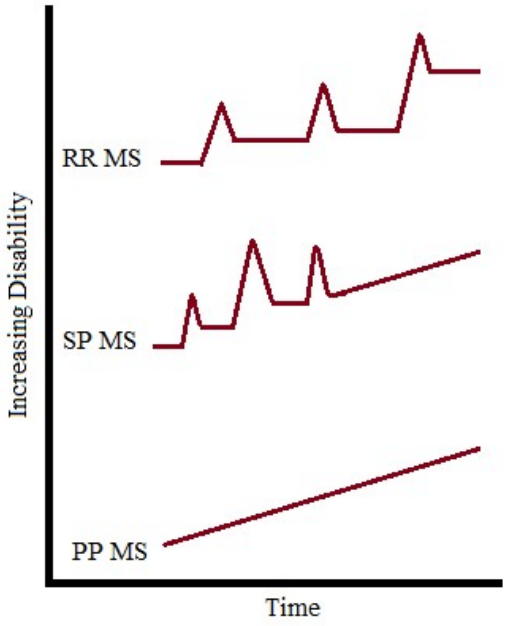
Lublin and colleagues (2014) published revised criteria for MS phenotypes. They recommended conceptualizing MS as either relapsing remitting or progressive with further distinction of the progressive disease as SPMS or PPMS. RPMS was excluded from the updated lexicon. The authors cautioned against using the terms malignant and benign due to insufficient clarity. Clinically isolated syndrome (CIS) was introduced as a distinct phenotype and a description was provided for a phenomenon termed radiologically isolated syndrome (RIS). Updated phenotypes and description of RIS are summarized in Table 1.1.

The most common phenotype is RRMS (Noseworthy et al., 2000; Widener, 2007). People with RRMS experience exacerbations of negative neural signs and symptoms and subsequently enter a remission phase in which the level of disability remains steady (Lublin et al., 2014). After 10-15 years of experiencing RRMS, most people transition to SPMS (Dobson & Giovannoni, 2019) in which periods of increased disability occur without remission (Lublin et al., 2014). Because RIS is a newly introduced concept and not yet considered a distinct phenotype (Lublin et al., 2014), data

regarding prevalence are lacking. Prevalence estimates for CIS are also lacking. However, a study on incidence of CIS in a multiethnic sample showed that incidence is higher Blacks and Caucasians and lower in Hispanic and Asian populations in the United States (Langer-Gould, Brara, Beaber, & Zhang, 2014).

Table 1.1: Summary of MS Phenotypes. (Lublin et al., 2014)

Phenotype	Description
Relapsing-remitting (RRMS)	Unpredictable episodes of disability that may or may not leave permanent impairments followed by periods of remission
Secondary-progressive (SPMS)	Initial course of RRMS that is followed by periods of increased disability without periods of remission
Primary-progressive (PPMS)	Steady increase in disability that begins at disease onset without acute exacerbations or periods of remission
Clinically Isolated Syndrome (CIS)	First clinical presentation showing characteristics of inflammatory demyelination
Radiologically Isolated Syndome (RIS)*	Incidental imaging findings suggest inflammatory demyelination in the absence of symptoms



* Authors do not currently recommend RIS as a distinct phenotype due to lack of prospective research in cohorts with this suspected condition.

Fatigue

Fatigue has been described as a complex, multifactorial symptom defined as a subjective lack of physical and/or mental energy that is perceived by the individual or

caregiver to interfere with usual and desired activities (Multiple Sclerosis Council for Clinical Practice Guidelines, 1998). This general feeling of lassitude is commonly called primary fatigue and is one of the most common symptoms of MS (Rohit Bakshi, 2003; R. Bakshi et al., 2000; Fiest et al., 2016; Fisk, Pontefract, Ritvo, Archibald, & Murray, 1994; L. Krupp, 2006; L. B. Krupp, Alvarez, LaRocca, & Scheinberg, 1988; L. B. Krupp, Serafin, & Christodoulou, 2010).

Reports of prevalence for MS-related, primary fatigue vary, likely due to variations in research methodology. The Multiple Sclerosis International Foundation reports that up to 95% of people with MS experience fatigue and that 55% report it as the most disabling symptom (Mills, 2012). Primary fatigue is more common in progressive forms of the disease than in RRMS (Johansson, Ytterberg, Hillert, Holmqvist, & von Koch, 2008; Lerdal, Gulowsen Celius, Krupp, & Dahl, 2007; Mills & Young, 2010; Rooney, Wood, Moffat, & Paul, 2019) and is associated with increased pain (Kahraman, Özdoğar, Ertekin, & Özakbaş, 2019), depression (Flachenecker et al., 2002; Greeke et al., 2017), and poorer scores in quality of life (QOL) measures (Barin et al., 2018; Berrigan et al., 2016; Janardhan & Bakshi, 2002; Mäurer et al., 2016; Simpson et al., 2019). There is a lack of agreement on the strength of the relation between fatigue and disability (Rohit Bakshi, 2003; Hadjimichael, Vollmer, Oleen-Burkey, & North American Research Committee on Multiple, 2008) . This could be attributed to use of varied research methods and outcome measures such as the Expanded Disability Status Scale (EDSS) that may lack sensitivity in comprehensively measuring the complex interaction among impairments, activity limitations, and participation restrictions associated with disability.

It is important to distinguish primary fatigue from secondary fatigue and muscular fatigue, both of which can be experienced by those with MS. Secondary fatigue is associated with factors that are not attributed solely to MS such as insomnia, medication use, and depression (Johnson, 2008; Kos, Kerckhofs, Nagels, D'Hooghe, & Ilsbroukx, 2007; Langeskov-Christensen, Bisson, Finlayson, & Dalgas, 2017) . Muscular fatigue has been defined as a temporary decrement in the capability of a muscle or muscle group to produce force (Enoka & Stuart, 1992; Gandevia, 2001; J. L. Taylor, Todd, & Gandevia, 2006). It has been suggested that the trait of primary MS fatigue to be referred to as "fatigue" and the state of decreased force production referred to as "fatigability" (Kluger, Krupp, & Enoka, 2013) and this terminology has been used with increased frequency in recent literature (Aldughmi, Bruce, & Siengsukon, 2017; Proessl, Ketelhut, & Rudroff, 2018; Severijns et al., 2017; Zijdewind, Prak, & Wolkorte, 2016).

Although muscular fatigability and primary fatigue are conceptualized as different symptoms of MS, they may be weakly associated. A recent meta-analysis reports a correlation of 0.31 (95% CI = 0.21, 0.41) between the two constructs (Loy, Taylor, Fling, & Horak, 2017). Investigators have found that those with MS who report greater levels of primary fatigue are also more susceptible to muscle fatigue in the first dorsal interosseous (Steens et al., 2011; Thickbroom et al., 2006; Wolkorte, Heersema, & Zijdewind, 2015) and quadriceps femoris muscle groups (Andreasen, Jakobsen, Petersen, & Andersen, 2009). Another research team examined motor evoked potentials (MEP) elicited via transcranial magnetic stimulation (TMS) before and after a fatiguing handgrip task in people with MS. They found that those who reported higher levels of primary fatigue took longer to return to a normal motor threshold for response to magnetic

stimulation (Liepert, Mingers, Heesen, Bäumer, & Weiller, 2005). Evidence supports the notion that decrements in inhibitory control may underlie this association (Leocani et al., 2001; Liepert et al., 2005). However, these findings are not consistent. Several studies have found no significant association between subjective measures of primary fatigue and muscle fatigue in the ankle dorsiflexors (Ng, Miller, Gelinas, & Kent-Braun, 2004) and muscles involved in handgrip (Iriarte & de Castro, 1998).

Comprehensive, specific mechanisms of primary MS fatigue remain unknown. However, evidence suggests that the primary pathological process of MS, including axonal damage and inflammation, contribute to the symptom (Kos et al., 2007; Langeskov-Christensen et al., 2017; Tartaglia et al., 2004; Vucic, Burke, & Kiernan, 2010). Targaglia and colleagues (2004) performed a retrospective analysis of people with MS who had undergone MRI spectroscopy and completed the Fatigue Severity Scale (FSS), a subjective measure of primary fatigue. They discovered that higher measures of primary fatigue were correlated with lower levels of N-acetylaspartate, a marker of neural integrity.

Motor Function

Multiple aspects of motor function can be negatively affected by MS. A common symptom is muscle weakness (Motl, Snook, & Schapiro, 2008; Ng et al., 2004; Widener, 2007) that often affects one side of the body more than the other (Confavreux & Vukusic, 2008). Weakness can be attributed to both primary CNS damage and secondary changes due to limited activity (Widener, 2007). In addition to of weakness, people with MS may

experience additional issues impairing muscle function including spasticity, tremor, and ataxia (Thompson, Baranzini, et al., 2018; Widener, 2007). These muscular abnormalities, combined with other impairments of body structures and functions, such as impaired somatosensation, can contribute to activity limitations that include problems with gait and balance (Cameron & Lord, 2010; Cameron & Nilsagard, 2018). People with MS are more likely than their healthy peers to fall while walking (Cameron & Nilsagard, 2018) and more and are more likely to sustain injuries as resulting from a fall (Mazumder, Murchison, Bourdette, & Cameron, 2014).

A meta-analysis of 32 studies contrasted gait characteristics between people with MS and healthy peers (Comber, Galvin, & Coote, 2017). This secondary analysis reported mean values for typical kinematic gait characteristics, confirming that MS is associated with differences that result in less stable gait. Typical gait in MS is characterized by a slower gait velocity, slower cadence, shorter step and stride lengths, increased step width, additional time spent in double limb support, less time in the swing phase, and longer stride time. These average kinematic parameters summarized by Comber (2017) were measured in laboratory settings, not in a natural environment. Another research team reported that MS not only affects laboratory-based measure of gait, but that these impairments are more pronounced in a natural, as opposed to laboratory, environment (Storm, Nair, Clarke, Van der Meulen, & Mazzà, 2018). Furthermore, variability of kinematic parameters is greater in people with MS than in healthy controls (Socie, Motl, Pula, Sandroff, & Sosnoff, 2013).

Postural control has been described as the action of controlling the body's position in space for the purposes of orientation and stability (Shumway-Cook &

Woollacott, 2012) and the act of maintaining, achieving, or restoring the center of gravity within one's base of support (Pollock, Durward, Rowe, & Paul, 2000). This construct is often impaired in those with MS (Alpini et al., 2012; Cameron & Lord, 2010; Cameron & Nilsagard, 2018; Kasser, Jacobs, Foley, Cardinal, & Maddalozzo, 2011; Prosperini & Castelli, 2018; Prosperini et al., 2013) and impaired postural control is associated with falling (Cameron & Lord, 2010; Kasser et al., 2011; Mazumder et al., 2014; Sosnoff et al., 2011).

Researchers have determined that people with symptomatic MS experience impaired motor function of the upper extremities (Carpinella, Cattaneo, & Ferrarin, 2014; Pellegrino, Coscia, Muller, Solaro, & Casadio, 2018; Quintern et al., 1999; Thickbroom et al., 2006; Wolkorte et al., 2015), as do people with CIS and asymptomatic MS (Solaro et al., 2007). However, studies examining the relation between upper and lower limb impairment in MS are lacking. A recent study by Coghe and colleagues (2019) reported kinematic profiles of people with MS performing two different motor tasks involving the upper or lower extremities and found that both upper and lower limbs are increasingly impaired as MS progresses. Although related, the upper and lower extremity impairments in their sample were only moderately related. It is interesting to note that the degree of motor control required to complete the tasks in Coghe may have influenced their results. For the lower extremity task, they selected steady-state gait, a continuous task influenced by central pattern generators that coordinate movement across all four limbs using sensory feedback (Guertin, 2013; Shumway-Cook & Woollacott, 2012). The upper extremity task was bringing the hand to the mouth, a discrete task in which feedforward

control is more important in successful execution of the task. Thus, this dissertation examined both upper and lower extremity task performance in people with MS.

Adequate motor control of the ankle is important to postural control during quiet standing. Although muscles of multiple joints work together (Reimann & Schöner, 2017), ankle musculature plays a particularly important role in managing small perturbations (Gatev, Thomas, Kepple, & Hallett, 1999; Horak & Nashner, 1986; Runge, Shupert, Horak, & Zajac, 1999). Therefore, experiments in this dissertation employed tasks in which the steadiness of the tibalis anterior, a primary dorsiflexor involved in the ankle strategy of postural control, was examined under two conditions, one in which a participant's focus was on maintaining steadiness of the contraction and another in which attention was divided between maintaining steadiness and completing a cognitive task.

Cognitive Function

Cognitive dysfunction is a common symptom of MS. It is estimated that up to 70% of people with MS experience some form of cognitive impairment (Amato, Zipoli, & Portaccio, 2006; Chiaravalloti & DeLuca, 2008; Rao, Leo, Bernardin, & Unverzagt, 1991). Furthermore, cognitive impairment can be observed in those with CIS, the earliest presentation of the disease (Anhoque, Domingues, Teixeira, & Domingues, 2010; Moghadam, Moayed, Sahraian, & Ameli, 2014). Cognitive dysfunction has traditionally been underdiagnosed (Benedict & Zivadinov, 2011; Chiaravalloti & DeLuca, 2008), in part due to the tendency for patient-reported problems of cognition to be confounded by primary fatigue and depression (Benedict et al., 2005; Carone, Benedict, Munschauer,

Fishman, & Weinstock-Guttman, 2005; Chiaravalloti & DeLuca, 2008; Rao et al., 1991). It may also be overlooked because it is not readily observable in most patients (Benedict & Zivadinov, 2011).

Although cognitive impairment itself detracts from a patient's quality of life, its presence in the early stages of MS is also associated with more rapid disease progression. People with CIS and cognitive impairment are more likely to convert to full MS than those with CIS who do not experience cognitive dysfunction (Zipoli et al., 2010). Furthermore, when cognitive impairment is present in those newly diagnosed with RRMS, the progression to greater levels of disability and progression to SPMS is hastened (Moccia et al., 2016).

Cognition is a construct that poses measurement challenges in both clinical practice and research. Studies comparing patients with and without cognitive impairment typically classify patients based upon performance thresholds from a variety of measures that assess different aspects of cognition (Sumowski et al., 2018). This results in varied operational definitions in the literature. The presentation of cognitive dysfunction in an individual with MS is variable and can affect multiple facets of cognition including episodic and working memory, executive functions of abstract reasoning and problem solving, attention, concentration, language functions, and visuospatial skills (Benedict & Zivadinov, 2011; Bobholz & Gremley, 2011; Chiaravalloti & DeLuca, 2008). Slowed information processing speed has been well documented in people with MS (Archibald & Fisk, 2000; DeLuca, Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004; Demaree, DeLuca, Gaudino, & Diamond, 1999; Moccia et al., 2016) and may contribute to other cognitive impairments (Costa, Genova, DeLuca, & Chiaravalloti, 2017).

Working memory is the process of temporarily storing information while simultaneously performing some other cognitive task such as reading or solving a problem (Baddeley, 1983). Working memory can be impaired in people with CIS (Anhoque et al., 2010) and MS (Archibald & Fisk, 2000; Bobholz & Gremley, 2011; Chiaravalloti & DeLuca, 2008; D'Esposito et al., 1996; Nelson et al., 2017).

Baddeley and Hitch (1974) first introduced the notion of a multicomponent working memory system by conducting a series of experiments to test the prevailing theory of the time. During this era, it was believed that working memory was an interplay between short and long term memory storage. However, Baddeley and Hitch believed this notion inadequate to explain the complexity of working memory and supported this idea with their findings from experiments in which participants were presented with isolated letters of the alphabet to remember, followed by reasoning tasks in which the letters needed to be recalled (Baddeley & Hitch, 1974). In addition to their experiments, the idea of a multicomponent working memory system was supported by the clinical observation that patients with impaired short term memory could manage information processing demands associated with working memory with minimal difficulty (Baddeley, 1983).

The Baddeley & Hitch model of working memory has three primary components, the central executive, phonologic loop, and visuospatial scratch-pad or sketchpad. The central executive is a limited-capacity processor that coordinates information distributed to the phonologic loop and visuospatial sketchpad that maintain auditory and visual information, respectively (Baddeley, 1983). The phonologic loop and visuospatial sketch pad are considered to be “slave systems” as they are responsible for maintaining

information directed to them from the central executive. The model has been refined to add another slave system, the episodic buffer, capable of holding chunked information that combines visual and auditory information with other sensory information such as taste or smell (Fig 1.2) (Baddeley, 2010). People with MS have been shown to have deficits in both the central executive (D'Esposito et al., 1996; Schulz, Kopp, Kunkel, & Faiss, 2006) and slave systems (Rao et al., 1993; Schulz et al., 2006) of working memory.

The multicomponent model of working memory provides opportunities to examine the visuospatial sketch pad, phonologic loop, and episodic buffer with various experimental tasks. However, working memory and its subcomponents cannot be dissociated from information processing speed. Tasks used to measure working memory typically require participants to attend to a task, process stimuli, and generate appropriate responses. Thus, a general impairment in processing speed can influence measurement of a specific component of working memory. This is an important consideration because strong evidence supports the notion that people with MS have slower processing speed than their healthy peers (Archibald & Fisk, 2000; Costa et al., 2017; Forn, Belenguer, Parcet-Ibars, & Ávila, 2008; Genova, Lengenfelder, Chiaravalloti, Moore, & DeLuca, 2012) and studies in populations with MS have revealed that processing speed is a greater contributor to cognitive impairments than working memory alone (Chiaravalloti, Stojanovic-Radic, & Deluca, 2013; DeLuca et al., 2004; Genova et al., 2012).

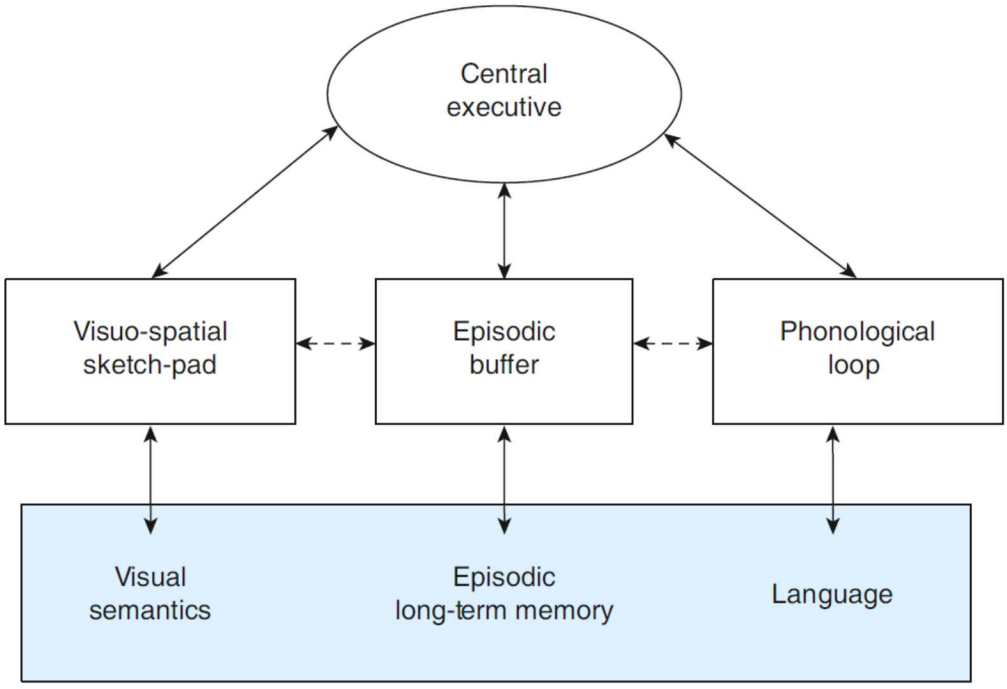


Figure 1.2. Multicomponent Model of Working Memory: Revision of Baddeley & Hitch's multicomponent model of working memory. The revised model includes a central executive component that distributes attention across three slave systems including the phonologic loop, visuospatial sketch pad, and episodic buffer. The episodic buffer was not included in the original model. Figure from Baddeley (2010).

The PASAT, one part of the MSFC, was first used to describe the initial effects of mild traumatic brain injury on information processing speed (Gronwall & Sampson, 1974). This task is considered to be a measure of both working memory and processing speed (Chiaravalloti et al., 2013; Fisk & Archibald, 2001). It is typically administered using a voice recording that provides a stimuli of a single-digit numbers delivered at a specific rate of speed. Respondents are asked to state the sum of the two most recently presented stimuli. The MSFC version of the PASAT presents stimuli every three seconds with an optional task of stimulus presentation at two-second intervals (Fischer, Rudick, Cutter, & Reingold, 1999).

The PASAT challenges working memory because respondents must hold one number in memory while performing an addition task and retrieve it to perform the next mathematical operation when the subsequent stimulus is presented. The task also addresses processing speed since the rate at which stimuli are presented can be manipulated using different interstimulus intervals. Although both working memory impairment and slowed information processing contribute to lower scores on the PASAT in people with MS, information processing is believed to be the primary factor by some (Forn et al., 2008), while others argue that the PASAT is too complex to be conceptualized as a simple measure of processing speed (Costa et al., 2017).

Quality of Life

It is important to not only understand specific impairments of body structures and functions associated with MS, but also to conceptualize the cumulative effect of these impairments on quality of life in a specific individual. A person with MS can experience any combination of previously mentioned clinical factors in varying degrees of severity. This may impact the activities a patient attempts and the manner in which he or she participates in daily life. It is reasonable to surmise that these impairments can contribute to psychosocial aspects of the disease.

People with MS generally have lower scores than healthy peers on quality of life measures (Goverover, Chiaravalloti, & DeLuca, 2016), a higher prevalence of depression (Feinstein, Magalhaes, Richard, Audet, & Moore, 2014), a greater risk of suicide (Brenner et al., 2016; Feinstein & Pavisian, 2017), and are more likely to experience

financial hardship (Jones, Pike, Marshall, & Ye, 2016; Maroney & Hunter, 2014; Thormann et al., 2017). A study examining data from 2013 calculated costs of MS-related care in the United States determined that total annual costs of managing and monitoring MS in a single patient range between $51,875 and $61,117, with higher costs associated with those who have more severe symptoms (Jones et al., 2016) as determined by the EDSS score.

Disease Specific Measures

Because clinical signs and symptoms of MS span a range of impairments, disease-specific tools have been developed to measure the summary effects of the disease. Measures commonly used in clinical practice and research include the Expanded Disability Status Scale (EDSS), the Patient-Determined Disease Steps Scale (PDDS), Multiple Sclerosis Functional Composite (MSFC), and the Functional Assessment of Multiple Sclerosis (FAMS). Each of these tools provide a measure of function or disability related to MS.

Expanded Disability Status Scale (EDSS)

The EDSS is a common measure of MS-related disability. EDSS scores are based upon a neurological examination, traditionally administered by neurologists who specialize in MS, of eight functional systems categorized as pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, and a category labeled “other” that includes any neurologic signs not captured during the examination of the other

functional systems. These functional system examination findings are converted to a ten-point ordinal scale in which higher scores indicate greater disability. The scale is anchored by scores of zero, normal neurological examination, and ten, death due to MS.

EDSS scores are strongly influenced by walking ability with scores between 0 and 4.5 ascribed to people who can ambulate without assistive devices. Higher scores indicate increased reliance on assistive devices for ambulation and activity limitations (Kurtzke, 1983). The EDSS has been shown to lack responsiveness to change in disease status (Bethoux & Bennett, 2011; Sharrack, Hughes, Soudain, & Dunn, 1999). Furthermore, EDSS scores and increased lesion load do not correlate for patients experiencing RRMS, an early stages of the disease, but do correlate as the disease progresses to SPMS (Truyen et al., 1996).

Patient Determined Disease Steps (PDDS)

The Disease Steps (DS) tool was introduced in 1995 as a simple, reproducible, ordinal measurement of disability designed to specifically capture ambulation ability, the most recognizable motor system impairment associated with MS (Hohol, Orav, & Weiner, 1995). Scores on the DS and EDSS were strongly correlated in the sample used to validate the measure (Hohol et al., 1995) and change scores between the two measures were moderately correlated after one year (Hohol, Orav, & Weiner, 1999). DS scores were based upon patient history and a neurological examination and anchored at scores of 0, normal neurologic function, and 6, confined to wheelchair (Hohol et al., 1995).

The Patient Determined Disease Steps (PDDS) scale is a valid, patient-reported outcome measure of MS-related disability (Learmonth, Dlugonski, et al., 2013). It has been argued that the PDDS is a suitable alternative to the EDSS (Marrie & Goldman, 2007). It is an ordinal measure that is administered as a single-item questionnaire in which a person with MS selects the single category that best describes his or her walking impairment due to MS. Scores range from 0, normal activity, to 8, bedridden. The PDDS is included in global patient registry of the North American Research Committee on MS (NARCOMS) (Vollmer, Ni, Stanton, & Hadjimichael, 1999) and investigators have begun to use it in lieu of the EDSS as a primary outcome measure (Briggs, Gunzler, Ontaneda, & Marrie, 2017; Duff et al., 2018; Fitzgerald et al., 2018; Pöttgen et al., 2018; Rizzo, Hadjimichael, Preiningerova, & Vollmer, 2004; Silveira & Motl, 2019; Wang et al., 2018; Weinkle et al., 2019). The PDDS has also been used to specify participation criteria when the EDSS was used as an outcome measure of disability (Coote et al., 2017).

Multiple Sclerosis Functional Composite (MSFC)

The MSFC is the product of an international task force convened in 1994 by the National MS Society of the United States. The task force was charged with developing a multidimensional clinical tool that was sensitive to change, avoided ceiling effects in greatly affected individuals, and included a measure of cognitive function, an aspect of MS that had not been included in other measures widely available at the time (Cutter et al., 1999; Rudick et al., 1996). Their final product, the MSFC, includes three simple,

objective clinical measures, converted to z-scores, that represent a composite snapshot of function (Fischer, Rudick, et al., 1999).

The three dimensions assessed by the MSFC include leg function, arm function, and cognition. Leg function is measured by recording the number of seconds required to walk 25 feet (25FWT). Arm function is measured by recording the number of seconds required to complete the 9-hole peg test (9HPT) in which participants grasp, place, and release pegs about a standard peg board as quickly as possible with a single hand. Cognition is measured by administering the Paced Auditory Serial Addition Test (PASAT) in which audio recordings of 60 single-digit numbers are presented at 3-second intervals for three minutes. On the PASAT, participants continuously state the sum of the last two digits presented. The PASAT outcome is the number of correct responses.

Because the three domains of the MSFC use different measurement units (time in seconds and number of correct responses) and directionality (higher scores indicate better performance on PASAT, but worse performance in 9HPT and 25FWT), domain scores are converted to z-scores for each component and a composite scores is then calculated (Cutter et al., 1999; Fischer, Rudick, et al., 1999). Lower MSFC scores indicate a greater degree of impairment than higher scores.

The MSFC has strong interrater and intrarater reliability (Cohen et al., 2000). Cutter et al. (1999) reported a moderate, inverse relation ($r = -.47$) between EDSS and MSFC composite scores with the strongest association between 25FWT and EDSS ($r = -.52$). The stronger relation of EDSS to 25FWT than to PASAT and 9HPT has subsequently reported by other investigators (Cohen et al., 2001; Cohen et al., 2000;

Hoogervorst, Kalkers, Uitdehaag, & Polman, 2002; Kalkers et al., 2000; Ozakbas, Cagiran, Ormeci, & Idiman, 2004) .

Additional evidence suggests that the cognitive aspect of the MSFC is not adequately assessed by simply reporting the number of correct responses on the PASAT. Some patients use a chunking strategy in which they skip some responses, effectively easing the cognitive burden of the task and possibly changing the underlying cognitive process used to complete it (Fisk & Archibald, 2001). This does not negatively affect internal validity of research studies using the MSFC but suggests that investigators and clinicians who wish to obtain a comprehensive measure of cognitive function should administer additional tests.

Diagnostic Criteria

A definitive diagnosis of MS cannot be based only the presence of clinical signs and symptoms. Although diagnostic criteria for MS have evolved with advances in knowledge and technology, all iterations include consideration of a patient's subjective history with imaging evidence of at least two visible areas of plaque formation in the central nervous system (CNS), observed at two distinct time points, referred to as dissemination of lesions in time and space. Furthermore, a diagnosis of MS should not be made unless other conditions that could better explain examination findings are ruled out (Brownlee, Hardy, Fazekas, & Miller, 2017; De Angelis, Brownlee, Chard, & Trip, 2019; Lublin et al., 2014; McDonald et al., 2001; Polman et al., 2011; Polman et al., 2005; Poser et al., 1983).

Table 1.2 summarizes the 2017 McDonald criteria, the most current diagnostic standards for MS. These revised recommendations include biomarker screening of cerebrospinal fluid for the presence of oligoclonal bands of immunoglobulin G (IgG) with electrophoresis, CNS imaging to visualize lesions, and a thorough review of a patient's history. The notable departure from prior criteria is the recommendation to diagnosis MS based upon a single episode of neurologic symptoms as long as the episode is accompanied by the presence of IgG in cerebrospinal fluid (CSF) (Thompson, Banwell, et al., 2018; Thompson, Baranzini, et al., 2018).

Because MS is a progressive neurodegenerative disease, it is commonly accepted that it is desirable to have patients begin disease-modifying medications to slow the rate at which symptoms and irreversible CNS damage present. The 2017 McDonald criteria revisions have expedited the diagnosis of MS resulting in earlier intervention with disease modifying drugs (Mantero, Abate, Balgera, La Mantia, & Salmaggi, 2018). Research studies comparing diagnoses made using both the 2010 and 2017 McDonald criteria in the same cohort of patients found the 2017 criteria to be more sensitive in detecting MS (Lee, Peschke, Utz, & Linker, 2019; Schwenkenbecher et al., 2019; van der Vuurst de Vries et al., 2018). Schwenkenbener and colleagues (2018) conducted a systematic review that applied the two iterations of the McDonald criteria to pooled patient data. They determined that 37% of patients would be diagnosed with MS using the 2010 criteria as compared to 68% diagnosed using the 2017 criteria. However, as sensitivity increased, specificity decreased (Lee et al., 2019; Schwenkenbecher et al., 2019; Solomon, Naismith, & Cross, 2019; van der Vuurst de Vries et al., 2018), potentially leading to an increased rate of false positive diagnoses.

Table 1.2: Diagnostic Criteria for MS. Summary of 2017 McDonald Criteria (Thompson, Banwell, et al., 2018)

Number of Clinical Episodes*	**Imaging Evidence at Time of Clinical Episode**	**Additional Criteria**
≥2	Evidence of ≥2 lesions **OR** A single lesion with historical evidence of a prior lesion in a different area	None
≥2	Evidence of 1 lesion	Additional clinical episode affecting a different location in the CNS **OR** ≥1 lesion in an area of CNS associated with MS lesions**
1	Evidence of 2 lesions	Additional report of previous clinical episode **OR** ≥2 lesions in MS-associated areas** **OR** presence of oligoclonal bands in CSF
1	Evidence of 1 lesion	Additional report of previous clinical episode **OR** ≥1 lesion in MS associated area **AND** any of the following: simultaneous presence of asymptomatic lesion **OR** new lesion compared to baseline image taken at any time **OR** presence of oligoclonal bands in CSF

* A clinical episode is an attack or symptom flare-up lasting at least 24 hours.
** MS-associated lesion areas: periventricular, cortical, juxtacortical, infratentorial, or spinal cord

Submaximal Isometric Force Steadiness

Voluntary, goal-directed movement in humans begins with motor preparation and planning distributed throughout the cerebrum including the parietal, temporal (Gentili et al., 2011; Toni, Thoenissen, & Zilles, 2001), and frontal lobes with the occipital lobe contributing to intended movement dependent upon visual feedback (Gentili et al., 2011). When sufficiently stimulated, corticospinal neurons in the primary motor cortex (M1) conduct action potentials along axons that primarily synapse on lower motor neurons in the ventral horn of the spinal cord and interneurons of the spinal cord (Schieber & Baker,

2013). These corticospinal neurons ultimately activate motor units, the smallest unit of voluntary muscular activation, consisting of a single alpha motor neuron, also called a lower motor neuron, and the muscle fibers it innervates (Liddell & Sherrington, 1925; Sherrington, 1925). The amount of muscular force produced is influenced by both the number of motor units recruited and the rate at which these motor units discharge, with lower forces particularly influenced by rate coding, the frequency at which motor units discharge action potentials (De Luca, LeFever, McCue, & Xenakis, 1982; Enoka & Duchateau, 2017; Milner-Brown, Stein, & Yemm, 1973).

Isometric contractions occur when muscles produce force but do not change length (Neumann, 2009). Isometric contractions contribute to tasks requiring joint stability and most activities of daily living are performed at submaximal levels of force (Grabiner & Enoka, 1995). Steady, submaximal isometric contractions are performed during activities such as standing quietly or stabilizing a proximal limb segment as the distal segment moves. Excessive force fluctuation (unsteadiness) during such tasks could have undesired consequences.

Quantification of force fluctuation, force steadiness, can be conceptualized in two ways, using standard deviation (SD) or coefficient of variation (CV) (Enoka et al., 2003; Galganski, Fuglevand, & Enoka, 1993). SD is an absolute measure of force fluctuation and reflects the dispersion of sampled forces about a mean of the distribution of those forces. Thus, SD is influenced by the absolute magnitude of the force produced. When force production is low, SD is also low. When force production increases, SD increases. While SD is a measure of absolute fluctuation, CV is a relative measure that normalizes the SD to the mean force produced. In contrast to SD which is low at lower forces, CV

tends to be greatest at lower levels of force production (Enoka et al., 2003; Moritz, Barry, Pascoe, & Enoka, 2005; Tracy & Enoka, 2002; Tracy, Maluf, Stephenson, Hunter, & Enoka, 2005; Vanden Noven et al., 2014). The equation for calculating CV is listed here.

$$CV\ \% = \frac{SD\ (sample\ standard\ deviation)}{\overline{X}\ (sample\ mean)}\ X\ 100\%$$

Increased CV at low force targets is attributed to a low-frequency oscillating neural drive of 2-3 Hz that is influenced by descending corticospinal commands as well as afferent inputs (Negro, Holobar, & Farina, 2009; Negro, Yavuz, & Farina, 2016). This finding has been observed via analysis of motor unit discharge rates by intramuscular or surface EMG in muscles with smaller motor units well suited for precision control (Negro et al., 2009; Tracy et al., 2005) and in muscles with larger motor units (Jesunathadas, Klass, Duchateau, & Enoka, 2012; Negro et al., 2009). Additionally, the demand of visual processing increases variability at very low levels of force (Tracy, 2007). Although it is not known whether the low-frequency oscillations are a perturbation to neural drive or a strategy to precisely regulate CNS output, it is argued that these oscillations are not solely attributable to noise (Lodha & Christou, 2017).

Hamilton and colleagues (2004) examined force steadiness in muscles associated with the thumb, index finger, wrist, and elbow and found a positive association between force steadiness and strength. The elbow flexors, the strongest muscle group in their experiment produced the steadiest contractions in the stronger elbow extensors and wrist

flexors and the least steady contractions were produced by the smaller thumb extensors and abductors of the second digit. This suggests that stronger muscles with greater numbers of motor units are steadier than smaller muscles with fewer motor units. Interestingly, Tracy and colleagues (2007) examined force fluctuation in upper and lower extremity muscles of young and old adults using the first dorsal interosseous (FDI) of the hand, the elbow flexors and knee extensors. The weaker FDI was less steady than the larger muscle groups, but the strongest group, the knee extensors, were less steady than the elbow flexors. It can be argued that Tracy's findings show that strength and motor unit numbers contribute to, but are not solely responsible for, force steadiness. Tracy (2007) also found that older adults were less steady than younger adults only at very low forces of the first dorsal interosseus and not the larger muscle groups. This, combined with the findings reported by Negro (2009), suggest that precise control at low forces is particularly affected by neural impairments, possibly due to an inability to manage noise and converging synaptic inputs to the motor unit pools. Therefore, this dissertation sought to examine upper and lower extremity steadiness across a range of forces in upper and lower extremity muscles of a similar size.

Submaximal Isometric Force Steadiness in Multiple Sclerosis

Little is known about submaximal isometric force steadiness in people with MS. Five published studies have reported findings for steadiness of lower extremity muscles in people with MS (Almuklass et al., 2018; Arpin, Davies, & Kurz, 2016; Davies et al., 2015; Davies, Hoffman, Healey, Zabad, & Kurz, 2017; Gould et al., 2018). Despite functional relevance and the fact that upper extremity motor impairments in muscles of

the upper extremity and steadiness in any muscle group across a range of forces has not yet been explored in this population despite the func.

Steadiness of ankle muscles in people with MS has been reported in four studies. Two examined ankle plantar flexor steadiness at 20% MVIC during an isometric task (Arpin et al., 2016; Davies et al., 2015). One examined ankle plantar flexors and dorsiflexors at 10% and 20% MVIC (Almuklass et al., 2018). Another used a dynamic steadiness task in which participants used the plantar flexors to trace a force target displayed on an adjacent monitor (Davies et al., 2017). All four studies reported impaired steadiness in those with MS that was associated with gait impairments. Furthermore, Davies (2015) reported that a 14-week training program consisting of a general warm-up, balance exercises, and over-ground or treadmill walking improved both force steadiness and gait quality in people with MS. Table 1.3 summarizes the literature examining force steadiness of ankle musculature in people with MS.

Gould and colleagues (2018) hypothesized that intellectual capacity of people with MS influenced both the perception of fatigue and muscular fatigability and tested this hypothesis in an experiment involving the knee extensors. After completing assessments of cognition, participants performed 60 successive quadriceps contractions, 10-seconds in length, at 25% MVIC on both legs. Participants were instructed to hold each contraction as steady as possible during each 10-second trial. The investigators measured muscle fatigue and force steadiness. They did not observe relations among muscle fatigue, perceived fatigue, and cognition. However, they did find that force steadiness decreased at a greater rate in people with MS during the series of fatiguing contractions.

Table 1.3: Summary of Research Exploring Force Steadiness in Non-fatiguing Muscular Contractions in People with MS.

Study	MS Type	Muscle or muscle group	Task	MS CV (%) $\bar{X}$ (SD)	Compared to healthy controls
Almuklass (2018)	RRMS	Plantar flexors & dorsiflexors	30-sec trials 10% and 20% MVIC	Plantar flexors: 10%: 3.9(2.6) 20%: 3.0(1.9) Dorsiflexors: 10%: 4.6(5.5) 20%: 3.5(5.2)	No control group
Arpin (2015)	RRMS SPMS	Plantar flexors	20% MVIC	3.9 *	MS: Less steady, slower gait, slower cadence, impaired gait kinematics, weaker
Davies (2015)	RRMS SPMS	Plantar flexors	20% MVIC	Pre: 4.2* Post: 2.3*	MS less steady at baseline; 45% reduction in CV with training; no significant difference between groups after training
Davies (2017)	RRMS SPMS	Plantar flexors	Dynamic tracing task	**Normalized torque: 0.42* Nm/kg	MS less steady; slower gait speed, altered gait kinematics

*Inferred from figure. Specific values of data not provided.
** Normalized torque in Newton x meters/kilogram for dynamic steadiness task.

There is a paucity of research exploring force steadiness in people with MS, but findings are consistent. Submaximal force steadiness of lower extremity muscles is impaired in people with MS and is associated with impaired gait kinematics. Opportunities exist to further explore force steadiness, its mechanisms, functional consequences, and rehabilitation approaches in people with MS.

Dual Cognitive Motor Task Performance

Activities of daily living are rarely performed in isolation. They typically involve simultaneous performance of two or more tasks such as completing a retail transaction while maintaining quiet stance or carrying on a conversation while walking. Therefore, dual-task laboratory experiments have the potential to generate knowledge particularly useful in shaping clinical practice.

When two tasks are performed simultaneously, attentional demands are greater than if each task were performed alone and can lead to diminished performance of both tasks (Abernethy, 1988; Lajoie, Teasdale, Bard, & Fleury, 1993). The relative change in performance of each task is termed dual task effect (DTE) and can be quantified with the equations that follow (Kelly, Janke, & Shumway-Cook, 2010). Negative values indicate a dual-task cost in which there is a decrement in performance with the addition of a second task. Positive values indicate a dual-task benefit in which performance improves with an additional task (Plummer & Eskes, 2015). Therefore, it is important to be mindful of the functional implications of the direction of change in variables of interest.

It is appropriate to use this equation to examine variables in which larger scores indicate better performance, such as strength or number of accurate responses.

$$DTE\ \% = \frac{(dual\ task - single\ task)}{single\ task} \times 100\%$$

When lower scores indicate better performance, such as reaction time, force fluctuation, or speed, the previous equation is modified by adding a negative sign to the numerator.

$$DTE\ \% = \frac{-(dual\ task - single\ task)}{single\ task} \times 100\%$$

DTE calculations provide insight into performance changes of both tasks. However, publications reporting DTE often fail to address the effect on both tasks (Plummer & Eskes, 2015). For example, a common clinical measure, the cognitive timed-up-and-go test (TUGc), is structured in a way that allows simple calculation of the motor effect, but not the cognitive effect. The TUGc motor task involves performing the following series of actions as quickly as possible when given a verbal instruction to "go": rise from a chair, walk three meters, turn, return to the chair, and return to a seated position. The motor task is performed alone and repeated while counting backward by three (Shumway-Cook, Brauer, & Woollacott, 2000).

The DTE of cognition on motor performance of the TUGc can be easily calculated by comparing the time taken to complete the task under single task (action only) and dual task (action and counting) conditions. The cognitive cost is not easily calculated because the lengths of time for each condition differ so that poorer motor performance, increased time to task completion, results in more time to provide additional cognitive responses. Reporting the TUGc DTE solely upon the motor task performance only shows the effect of the cognitive challenge on motor performance. Even though motor performance is typically impaired with addition of a secondary task, the cognitive task could be impaired, enhanced, or unaffected. Each of these cognitive outcomes would be interpreted differently.

Plummer and colleagues (2013) described a conceptual framework (Figure 1.3) for classifying possible outcomes of dual task performances. These outcomes include four primary changes (motor task facilitation, motor task interference, cognitive task facilitation, cognitive task interference), combinations of these changes, and the possibility that no changes occur. The bottom, left quadrant represents mutual interference in which both the cognitive and motor tasks impair one another. This is the logical hypothesis for outcomes of dual task experiments in which both tasks are sufficiently challenging and demand attention of the performer. Mutual facilitation is an outcome that would be observed if both tasks were enhanced by simultaneous performance. Cognitive-priority tradeoff occurs when the cognitive measure improves, but the motor measure worsens under dual task conditios. The converse, motor-priority tradeoff, is also a possible outcome (Plummer, Villalobos, Vayda, Moser, & Johnson, 2014).

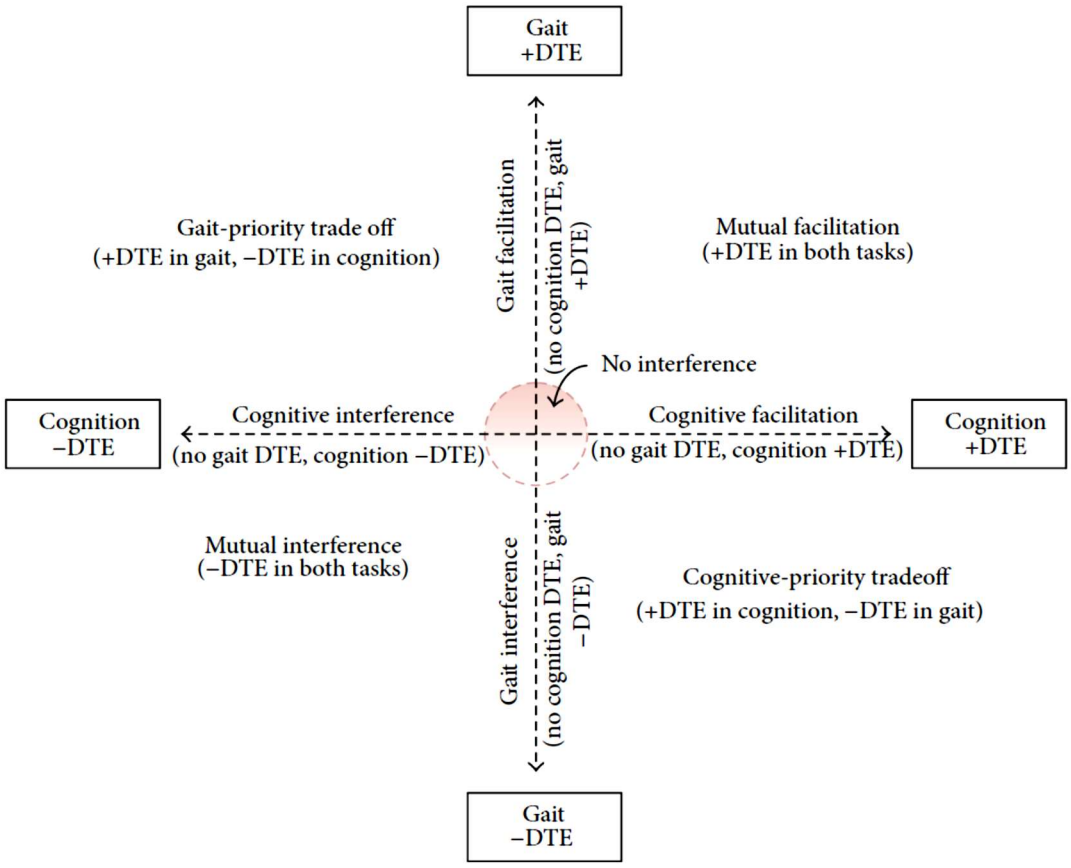


Figure 1.3: Patterns of Cognitive-Motor Dual Task Effects. Possible outcomes of a dual-cognitive task involving gait. Center (red circle) represents no dual task effect on cognition or gait. Mutual interference is illustrated in the bottom left quadrant, in which both tasks are impaired under dual task conditions. From Plummer (2014). Reprinted with permission of Prudence Plummer.

Dual Cognitive Motor Task Performance in Multiple Sclerosis

Inconsistent findings of DTE have been reported in studies of people with MS. This may be attributed to the variety of experimental tasks used in research or the varied levels of MS-related disability between samples. An additional confounding factor is that several studies report only the motor effects and not cognitive effects of experimental dual tasks.

A recent systematic review analyzed findings of 13 controlled studies that reported DTE with an emphasis on cognitive-motor interference (CMI), a decrement of both cognitive and motor task performances under dual task conditions. All but two studies had 95% confidence intervals that spanned zero indicating no difference between groups. The overall pooled effect revealed that both people with MS and healthy controls experience CMI. Further, it was noted that although people with MS experienced a greater degree of CMI than controls, differences were minimal (Learmonth, Ensari, & Motl, 2017).

Another systematic review of dual tasking examined the motor task of maintaining postural control while standing. Investigators reviewed 11 studies and found that only three reported CMI, two reported improved postural control with dual tasking, and nine reported a negative DTE of a cognitive task on the motor task of postural control. Unfortunately, several of the included studies did not report the DTE that the motor task exerted on cognitive performance (Chamard Witkowski, Mallet, Bélanger, Marrero, & Handrigan, 2019).

To date, no dual task studies in MS have used submaximal isometric force steadiness as a primary motor task. The most common motor tasks in dual task experiments include gait and static standing. Gait has been examined in the context of gait initiation, ambulation over short distances, and gait termination.

Two controlled studies examined gait initiation in people with CIS (Brecl Jakob, Remšak, Šega Jazbec, Horvat Ledinek, & Rot, 2017) and MS (Jacobs & Kasser, 2012). Both reported greater dual-task impairments in people with CIS or MS.

Gait over distances 25 feet or less is a common experimental motor task used in both controlled studies (Allali, Laidet, Assal, Armand, & Lalive, 2014; Coghe, Pilloni, et al., 2018; F. Hamilton et al., 2009; Kalron, Dvir, & Achiron, 2010; Learmonth, Pilutti, & Motl, 2015; Mofateh, Salehi, Negahban, Mehravar, & Tajali, 2017; Nogueira, Santos, Sabino, Alvarenga, & Thuler, 2013; Pau et al., 2018; Saleh et al., 2018; Sandroff, Benedict, & Motl, 2015; Wajda, Sandroff, Pula, Motl, & Sosnoff, 2013) and cohort studies (Chaparro et al., 2017; Etemadi, 2017; Fritz, Kloos, Kegelmeyer, Kaur, & Nichols-Larsen, 2019; Malcay, Grinberg, Berkowitz, Hershkovitz, & Kalron, 2017; Motl et al., 2014; Sosnoff et al., 2017; Wajda, Motl, & Sosnoff, 2013). Most, but not all, controlled studies in this review reported a greater negative DTE on motor performance in MS than in healthy controls. The most consistent observation was that during dual task conditions involving gait and a cognitive task, people with MS experienced greater declines in gait velocity (Allali et al., 2014; F. Hamilton et al., 2009; Kalron et al., 2010; Pau et al., 2018; Sandroff, Motl, Sosnoff, & Pula, 2015), cadence (Mofateh et al., 2017), and increased variability of step or stride lengths (Allali et al., 2014; F. Hamilton et al., 2009; Mofateh et al., 2017; Pau et al., 2018) than healthy controls. Three studies found no detrimental DTE of an added cognitive task on velocity or cadence in people with MS (Learmonth et al., 2015; Nogueira et al., 2013; Saleh et al., 2018). Finally, a study by Coghe and colleagues (2018), reported a positive association between decrements in motor performance of gait during dual tasking and general brain atrophy measured with MRI.

Uncontrolled studies using gait as a motor task explored associations between DTE on the motor task and other variables. Findings include an association between

greater negative DTE and increased fall risk (Etemadi, 2017) and level of disability (Sosnoff et al., 2017). An imaging study using functional magnetic resonance imaging (fMRI) reported a moderate association between supplementary motor area (SMA) activity and the calculated DTE of cognition on motor performance of the Timed-Up-and-Go test (TUG) (Fritz et al., 2019).

In addition to studying steady gait and gait initiation, gait termination has been explored. A controlled study asked participants to stop walking when presented with a verbal cue. Both healthy controls and those with MS experienced a negative DTE of cognition on the motor aspects of gait termination including altered kinematic parameters and increased time required to terminate gait. There were no significant differences in the DTE between groups with and without MS (Roeing, Wajda, Motl, & Sosnoff, 2015).

Quiet standing, a task of postural control, is another experimental task used in dual task designs of both controlled (Kalron, Dvir, & Achiron, 2011; Negahban et al., 2011; Prosperini et al., 2016; Prosperini et al., 2015; Ruggieri et al., 2018) and cohort studies (Boes et al., 2012; Etemadi, 2017) in people with MS. The controlled studies found greater negative DTEs on quiet stance in people with MS than controls. The cohort studies reported no association between level of disability and DTE (Boes et al., 2012). Cohort studies also reported increased fall risk associated with a negative DTE on cognition, but not the DTE on the motor task of quiet standing (Etemadi, 2017).

Most studies of DTE examined lower extremity motor function. However, activities of daily living also include motor tasks performed with the upper extremities. In this literature search, only one dual-task study was found in which an upper extremity motor task was used. Participants in a study by Learmonth and colleagues (2015)

performed the 9-hole peg test and a cognitive task of reciting alternate letters of the alphabet. They found that both healthy controls and those with MS experienced a negative DTE on motor performance when adding a cognitive task and that the magnitude of DTE was not different between the groups.

Cognitive tasks vary across studies and do not include the PASAT, a component of the MSFC. The most common cognitive tasks include word list generation (Malcay et al., 2017; Motl et al., 2014; Prosperini et al., 2016; Wajda, Motl, et al., 2013; Wajda, Sandroff, et al., 2013), Stroop tasks (Coghe, Fenu, et al., 2018; Coghe, Pilloni, et al., 2018; Jacobs & Kasser, 2012; Kalron et al., 2011; Prosperini et al., 2016; Prosperini et al., 2015; Ruggieri et al., 2018), reciting alternate letters of the alphabet (Chaparro et al., 2017; Learmonth et al., 2015; Roeing et al., 2015; Sandroff, Benedict, et al., 2015; Sosnoff et al., 2017) and serial subtraction tasks (Etemadi, 2017; Malcay et al., 2017; Mofateh et al., 2017; Negahban et al., 2011; Nogueira et al., 2013; Saleh et al., 2018; Sosnoff et al., 2017). Findings for motor DTE on cognitive task performances are not reported as frequently as motor effects associated with the addition of a secondary cognitive task. When these cognitive effects are reported, findings are inconsistent. Some studies reporting similar DTE on cognition in people with MS and controls (Prosperini et al., 2016; Roeing et al., 2015) and others report a greater negative DTE of motor task performance on cognition in MS (F. Hamilton et al., 2009; Saleh et al., 2018) and CIS (Brecl Jakob et al., 2017). This may be partially attributed to a lack of instructions to participants on how to prioritize dual tasks. Because falling is a consequence of failed attempts at static standing or gait perturbations, it is logical to surmise that participants would devote additional attention to the motor task. Without knowing how tasks were

prioritized in the literature, it is not possible to assume that effort was equally devoted to both tasks.

Studies of dual task performance in people with MS have typically been descriptive. However, a seminal study by D'Esposito and colleagues (1996) examined mechanisms of DTE in MS within a model of working memory (Baddeley, 1983). D'Espotio's primary task required participants to make a visual judgement about the orientation of two lines by either vocalizing the correct response or pointing to it. The secondary tasks included rapid finger tapping, repeatedly and accurately humming a lullaby, and repeatedly reciting the alphabet. There were no between group differences in single task performances for all four individual tasks. However, those with MS demonstrated a greater negative DTE for dual task line orientation judgement with all secondary tasks as well as a greater negative DTE on humming and reciting the alphabet in those with MS. Impairment on the orientation task was lowest for the finger tapping task in both controls and MS, presumably attributed to the fact that finger tapping without a target t requires little attention relative to accurate humming or reciting the alphabet.

D'Esposito (1996) also discovered that impaired DTE in people with MS was associated with neurological measures of executive functioning including the PASAT and symbol digit modalities test. Although the tasks used in this study differ from the cognitive-motor tasks previously addressed in this review, it provides evidence for impaired central executive functioning as a mechanism for dual task decrements in MS. The central executive of Baddeley's working memory model is responsible for managing attention across the subsystems of the phonologic loop, visuospatial sketch pad

(Baddeley, 1983, 1992), and episodic buffer (Baddeley, 2010). It therefore reasons that attentional capacity contributes to dual task performance.

The idea of attention required by a cognitive task has been explored in healthy populations. Loirst and colleagues (2002) asked healthy adults to perform an auditory choice reaction task and a steady, fatiguing, submaximal contractions at 5% and 30% MVIC of the first dorsal interosseus muscle under both single and dual task conditions. They observed CMI in dual task conditions that greatly increased with fatigue. Interestingly, this same group subsequently performed a similar study using the same methods in a high-effort, non-fatiguing task at targets of 30% and 60% of MVIC (Zijdewind, van Duinen, Zielman, & Lorist, 2006). CMI was observed in this study, especially at the higher target forces, but to a lesser degree than in the prior study specifically designed to fatigue the muscle even at the same target force of 30% MVIC. Because higher voluntary forces are produced via increased central drive, it is plausible that cortical information processing required to increase neural drive could divert attentional resources from the cognitive task to the high-effort motor task, especially when that task induces muscle fatigue. Although these studies included a sample of healthy adults, the mechanisms underlying CMI in this population may be helpful in conceptualizing CMI in those with MS.

Dissertation Aims and Hypotheses

Submaximal isometric force steadiness is required across a range of forces for successful completion of everyday tasks, yet it is unknown if multiple sclerosis affects

this aspect of motor behavior. Furthermore, the ability to simultaneously perform cognitive and motor tasks has not been fully examined in a population with multiple sclerosis. Two experiments were carried out to address the aims that follow.

The first study sought to determine isometric force steadiness of upper and lower extremity muscle groups, determine if a relation between upper and lower extremity steadiness existed, and compare these findings between people with MS and healthy controls. A secondary goal was to identify a steady, non-fatiguing force target for people with MS that could be successfully completed in the second experiment, an examination of dual task effects of cognitive and motor tasks. The muscles selected in this first experiment include the ankle dorsiflexors, key contributors to the ankle strategy to maintain postural control in standing, and the elbow flexors, for holding the distal hand and wrist steady for interaction with the environment.

The second study explored cognitive-motor task performance in people with multiple sclerosis and compared the findings to healthy controls. The cognitive task included a modified version of the PASAT, a measure of working memory and information processing speed. PASAT stimuli were delivered with interstimulus interval of 3-seconds and 4-seconds. The motor task selected was ankle dorsiflexion at a steady, non-fatiguing force identified in the first experiment.

Aim 1: To compare force steadiness during low-force, non-fatiguing isometric contractions between people with multiple sclerosis and healthy, age and sex matched peers.

- **Hypothesis 1a:** People with MS will be less steady across all ranges of force than healthy controls.
- **Hypothesis 1b:** All participants will demonstrate less steadiness at the lowest force targets of 2.5% and 5.0% MVIC in both the upper and lower extremities.

Aim 2: To determine if people with MS use a different motor control strategy to optimize steadiness as compared to healthy controls.

- **Hypothesis 2:** People with MS will use a co-contraction strategy more often that healthy controls.

Aim 3: To compare force steadiness between upper and lower extremity muscle groups in people with MS and compare these findings to healthy controls.

- **Hypothesis 3:** Force steadiness will be positively correlated between upper and lower extremity muscle groups to the same degree in people with and without MS.

Aim 4: To determine if dual task effects of performing a cognitive-motor task differ between people with and without MS.

- **Hypothesis 4a:** Both healthy controls and those with MS will experience cognitive motor interference, a decrement in both motor and cognitive performances, with dual tasks.
- **Hypothesis 4b:** Both healthy controls and those with MS will experience a greater cognitive dual task cost when processing time is shortened.
- **Hypothesis 4c**: People with MS will experience a greater negative dual task effect on cognition than healthy controls.

- **Hypothesis 4d:** People with MS will experience a greater negative dual task effect on force steadiness than healthy controls.

CHAPTER 2. SUBMAXIMAL ISOMETRIC STEADINESS OF THE UPPER AND LOWER EXTREMITIES IN PEOPLE WITH MULTIPLE SCLEROSIS

INTRODUCTION

Steady, submaximal, isometric contractions are required to perform everyday tasks. Force fluctuation has been well studied in healthy younger and older adults (Enoka et al., 2003; Galganski et al., 1993; Pereira et al., 2019; Pereira, Schlinder-Delap, Nielson, & Hunter, 2018; Pereira et al., 2015; Tracy, 2007; Tracy, Dinenno, Jorgensen, & Welsh, 2007; Tracy & Enoka, 2002; Tracy et al., 2005; Tracy, Mehoudar, et al., 2007; Vanden Noven et al., 2014; Yoon, Vanden Noven, Nielson, & Hunter, 2014) and less frequently studied in people with MS (Almuklass et al., 2018; Arpin et al., 2016; Davies et al., 2015; Davies et al., 2017; Gould et al., 2018) . Controlled studies of submaximal force steadiness in MS during non-fatiguing contractions have been limited to the ankle plantar flexors (Arpin et al., 2016; Davies et al., 2015) and one uncontrolled study that examined the ankle plantar flexors and dorsiflexors (Almuklass et al., 2018). At 20% MVIC, the ankle plantar flexors of people with MS are less steady than healthy controls and is associated with impairments in lower extremity motor control (Arpin et al., 2016; Davies et al., 2015). Exercise interventions targeted specifically at improving steady, submaximal, isometric contractions in people with MS not only improve steadiness (Davies et al., 2015) , but also gait (Davies et al., 2017). Therefore, examination, evaluation, and interventions involving steady, isometric contractions may benefit those with MS.

It is well known that MS is a chronic, progressive, autoimmune disorder in which a process of inflammation and demyelination progressively damages axons and myelin-producing oligodendrocytes of the central nervous system (Compston & Coles, 2008; Noseworthy et al., 2000; Sospedra & Martin, 2016). The resulting signs and symptoms depend upon the extent and location of the neural damage (Noseworthy et al., 2000), yet even those with asymptomatic MS have been found to have impairments in cognition (Schulz et al., 2006) and motor control (Kalron et al., 2011; Solaro et al., 2007). Coghe and colleagues (2019) attempted to determine the relation between upper and lower kinematics in people with minimal to moderate MS-related disability. They found that greater disability was associated with declines in upper and lower limb motor performance. Interestingly, there was only a moderate relation between upper and lower extremity impairment. Thus, the same autoimmune processes produce varied clinical presentations that involve both the upper and lower extremities, but it is not known whether upper and lower extremities are similarly affected by the general strain placed upon the CNS by disease related processes.

Tracy and colleagues (2007) examined force fluctuation in upper and lower extremity muscles of young and old adults using the first dorsal interosseous (FDI) of the hand, the elbow flexors and knee extensors. The relatively small FDI was less steady than the larger elbow and knee muscle groups and fluctuation between those two muscle groups were moderately associated for forces at or above 5% MVIC suggesting that the motor unit pools controlling these upper and lower extremity muscle groups is similarly affected by input from the CNS. Because MS affects the CNS and even asymptomatic patients may have motor impairments, it is reasonable to speculate that a CNS

impairment primarily affecting lower extremity motor control may also affect the upper extremity, as well as the converse.

No study has yet examined steadiness in the upper and lower extremities in people with MS across a range of forces. The purposes of this study were threefold. The first was to compare force steadiness during low-force, non-fatiguing isometric contractions between people with MS and healthy controls. The second was to determine if people with MS used a different motor control strategy than healthy controls. The third was to compare force steadiness between upper and lower extremity muscles in the same group of individuals. It was hypothesized that people with MS would be less steady across all forces in both the upper and lower extremities, that people with MS would exhibit a greater degree of agonist-antagonist co-activation during steady isometric contractions, and that lower and upper extremity force steadiness would positively associate within groups (MS and controls).

METHODS

Fifteen people with MS (5 males and 10 females; mean (SD): 49.7 (9.5) years; 168.6 (6.7) cm height, 80.2 (16.7) kg body mass) and fifteen healthy controls (3 males and 12 females; mean (SD): 47.2 (6.4) years; 167.3 (11.5) cm in height, 80.2 (16.8) kg in body mass) volunteered to participate. Volunteers were eligible if they were between the ages of 18 and 60 and could actively dorsiflex the left ankle and flex the left elbow through a full range of motion against gravity. Those with MS were eligible if disease progression was stable for at least six months. Participants were excluded if they lacked

sufficient visual acuity to see a computer monitor at a distance of 1.0 meter or experienced any condition other than MS that impaired function of the left ankle.

The experiment was conducted in a single session at Marquette University. Volunteers were oriented to the protocol and provided informed consent as approved by the university's Institutional Review Board (Protocol HR-3154).

Participants

Recruitment and Enrollment. Participants were recruited from an existing pool of volunteers who had previously completed research studies in our lab. People with MS were recruited at community events sponsored by the MS Society and at an area gym for people with MS. Advertisements were placed on social media sites and shared by local MS support groups. Prospective participants were screened for inclusion and exclusion criteria via phone or email and consecutively enrolled in the study.

Participant Characteristics. All participants completed a series of questionnaires to measure fatigue and depression and basic demographic information was obtained. Each participant provided his or her age, birth month, birth year, biologic sex, and number of years of secondary and postsecondary education completed. Height in cm and mass in kg were obtained with a stadiometer and digital scale, respectively. The trait of primary fatigue was measured with the Modified Fatigue Impact Scale (MFIS) (Rivito et al., 1997) and depression with the Centers for Epidemiologic Studies Depression Scale (CESD) (Radloff, 1977).

The MFIS is an ordinal scale measure of fatigue (Rivito et al., 1997). This questionnaire contains 21 items and total score ranges from 0-84, with higher scores indicating greater impact of fatigue on daily life. The measure also reports fatigue on three subscales, physical, cognitive, and psychosocial. The tool is included in the MS-Quality of Life Inventory (Fischer, LaRocca, et al., 1999; Rivito et al., 1997), a ten-item battery of questionnaires recommend for use by the United States' Multiple Sclerosis Society. Although the tool has adequate test-retest reliability (Kos et al., 2005; Larson, 2013) and correlates with other measure of fatigue (Flachenecker et al., 2002; Larson, 2013; Téllez et al., 2005), caution should be used when interpreting the measure as solely a measure of fatigue. Because MFIS scores may be confounded by depression (Larson, 2013) this study also included a measure of depression.

The CESD is an ordinal measure of depression developed for use in a the general population (Radloff, 1977). Scores on this 20-item questionnaire reange between 0-60, with higher scores indicative of depression. It is reliable in a population with MS (Verdier-Taillefer, Gourlet, Fuhrer, & Alpérovitch, 2001). Although debate exists on applying a cutoff score to make this ordinal scale measure a diagnostic screening tool, it is generally accepted that higher scores indicate depression in people with MS (Patten, Berzins, & Metz, 2010). It is a reliable measure in people with MS (Verdier-Taillefer et al., 2001).

Participants with MS completed disease-specific questionnaires to measure disability and quality of life. Questionnaires included the Patient Determined Disease Steps Scale (PDDS) (Learmonth, Motl, Sandroff, Pula, & Cadavid, 2013; Rizzo et al., 2004), a self-reported measure disability status and the Functional Assessment of

Multiple Sclerosis (FAMS) (Cella et al., 1996), a self-reported measure of quality of life. Both questionnaires asked specific questions pertaining to symptoms of MS and were therefore not applicable for completion by healthy controls. Participants with multiple sclerosis also provided the month and year of diagnosis, MS phenotype, and indicated which disease modifying medications were used at the time the experiment took place.

Multiple Sclerosis Functional Composite (MSFC). All participants completed the three tasks comprising the MSFC (Fischer, Rudick, et al., 1999). The two activity domain tasks in the MSFC include the 9-hole peg test (9HPT) and 25-foot walk test (25FWT). The cognitive domain was assessed via the Paced Auditory Serial Addition Test (PASAT).

The 9HPT, a measure of upper extremity function, was administered using standard procedures described in the MSFC guidebook using a Roylan 9-hole peg test board (Smith & Nephew, Germantown, WI). The time in seconds (s) required for participants to move nine pegs from a shallow well to placeholders and back to the well was recorded. Two trials were completed with the dominant hand followed by two trials with the nondominant hand. The mean of all four trials was recorded and used to calculated composite MSFC score and as a descriptive variable.

The 25FWT, a measure of lower extremity function and walking ability, was administered according to MSFC guidebook instructions. Participants walked 25 feet as quickly as could be safely managed in a private, unobstructed laboratory space. Participants were permitted to use walking aids if these assistive devices were also used during typical ambulation. The time in seconds (s) to walk 25 feet was recorded. The task was completed twice and mean of the two trials was recorded.

The PASAT, a measure of cognitive function, was administered following instructions in the MSFC guidebook. Subjects listened to an audio recording of single digit numbers that were presented every 3 seconds (PASAT-3). Subjects stated the sum of the two most recently presented digits. A practice block of 10 items was completed prior to scored trials. Participants completed at least one, but no more than three, practice blocks. Following the practice block, 60 digits were presented and the number of correct responses was recorded.

MSFC composite scores were calculated for participants with MS. Scores for individual components of the MSFC (9HPT, 25FWT, PASAT-3) were converted to z-scores to allow calculation of a composite MSFC score using the formula reported in the administration and scoring guidebook.

$$MSFC\ Score = \left\{ \frac{\bar{X}\left(\frac{1}{9HPT}\right) - .0439}{.0101} + \frac{-\bar{X}(25FWT) - 9.5353}{11.4058} + \frac{PASAT3 - 45.0311}{12.0771} \right\} / 3.0$$

Experimental Setup and Measures

Measures of Force. Experimental tasks were performed using the left ankle dorsiflexors and left elbow flexors. For both upper and lower extremity tasks, participants were seated upright in an adjustable chair with hips and knees flexed to 90°. Proximal body segments were secured to prevent accessory movements that could affect force measures. Limb length was recorded between the axis of the elbow or ankle joints and the point at which force was applied to the transducer to allow calculation of torque.

For the elbow flexion task, each participant placed the left elbow on a supportive pad with the shoulder in approximately 20° abduction and the forearm in anatomic neutral. The distal forearm and wrist were secured in a modified orthosis secured to a JR3 load cell (JR3, Woodland, CA) that was calibrated with known loads (kg) prior to the study. Force output was converted to a digital signal using a Power 1401 analog to digital convertor and sampled at a frequency of 500 Hz using Spike 2 software (Cambridge Electronic Designs, Cambridge, UK). The experimental setup for the elbow is depicted in Figure 2.1.

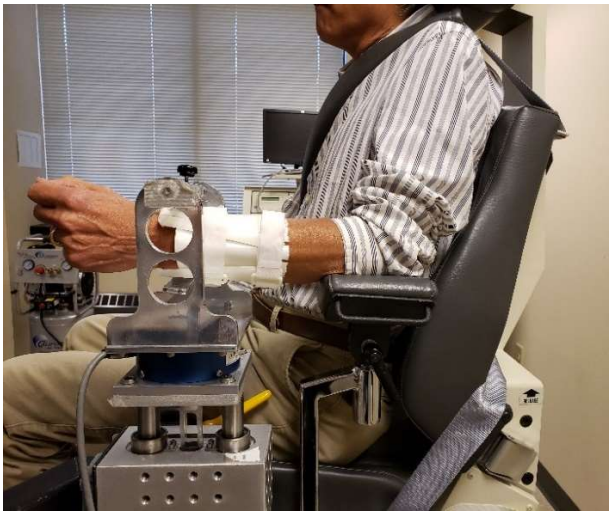


Figure 2.1. Experimental Setup for Elbow Force Measurement. Participants were seated in an adjustable chair with the left elbow resting on a padded support surface and the distal forearm and wrist in a modified orthosis secured to the measurement apparatus. Force was measured with a JR3 load cell, seen inferior to the wrist.

For the ankle dorsiflexion task, the left foot of each participant was secured to a footplate and secured with a firm hook-and-loop fastening strap placed just proximal to the metatarsal heads. A strap was also placed over the talocrural joint to secure posterior aspect of the heel to the footplate. Participants wore flat soled athletic shoes during testing and a thin foam pad was placed between the strap and shoelaces to prevent potential discomfort of the tightly secure strap from affecting effort.

Force output was measured with a custom strain gauge transducer (Transducer Techniques, Temecula, CA) that was calibrated with known weights (kg) prior to the study. Signals were amplified X100 and low pass filtered at 25 Hz using an amplifier (Grass Telefactor, Model P122, Warwick, RI). Force output was digitized using an analog to digital convertor, (CED 1401, Cambridge Electronic Designs, Cambridge, UK), sampled at 500 Hz, recorded, and saved for analysis using a custom program operated via Spike 2.7 (Cambridge Electronic Designs, Cambridge, UK). The experimental setup for the ankle is depicted in Figure 2.2.

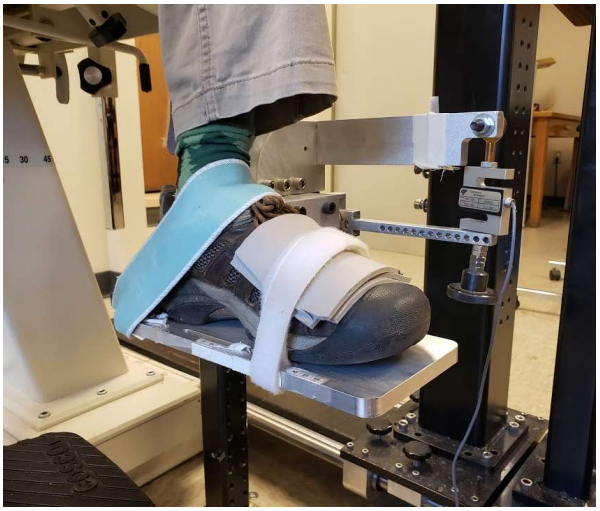


Figure 2.2. Experimental Setup for Ankle Force Measurement. Participants were seated in an adjustable chair with the left foot secured to a footplate. Force was measured with a customized strain gauge transducer, seen superior and to the right of the toe.

A 27” monitor was placed at eye level approximately 1 meter in front of the participant. The monitor displayed continuous force feedback over a 15-second window. The y-axis display remained constant across all targets as increased visual gain has been shown to positively affect force steadiness in muscles of the ankle and elbow (Prodoehl & Vaillancourt, 2010).

Electromyography. Whole muscle surface electromyographic (EMG) activity of primary agonists and antagonists was recorded and amplified (x1000) using a two-channel Delsys Bagnoli handheld EMG unit (Delsys, Natik, MA). EMG signals were recorded through a Power 1401 analog to digital convertor and sampled at 1 kHz using Spike 2 software. Delsys DE-2.1 differential surface electrodes (Delsys, Natik, MA) were used as recording electrodes. These recording electrodes contain two silver contacts, 1 cm in length and 1 cm apart, housed in a noise-shielding polyurethane shell. Recording electrodes were placed so points of contacts aligned perpendicular to fiber orientation of the target muscle. Disposable self-adhering Dermatrode electrodes (American IMEX, Irvine, CA) were used as ground electrodes. Prior to affixing electrodes, the skin was gently abraded and cleaned using electrode prep pads (Professional Disposables International, Orangeburg, NY).

EMG recording were made for the tibialis anterior and medial head of the gastrocnemius for ankle tasks and the biceps brachii and triceps brachii for elbow tasks. Recording and ground electrodes were placed on muscle bellies and bony landmarks in accord with recommendations by the Surface Electromyography for the Non-Invasive Assessment of Muscles (SENIAM) project (Hermens, Freriks, Disselhorst-Klug, & Rau, 2000) with the exception of the ground electrode placement for ankle tasks in which the ground electrode was placed on the patella. Noise was checked by collecting 5-10 seconds of data in which participants were instructed to relax the muscles of interest. Threshold for acceptable noise was set at 0.005 volts (V).

Experimental Protocol

The ankle dorsiflexion task was performed prior to the elbow flexion task. This order was chosen because a secondary aim of the study was to determine a steady, non-fatiguing ankle force level that could be used in the subsequent experiment involving dual task performance. As it was unknown how primary fatigue might affect those with MS over the duration of the experimental session, the ankle task was performed first.

Maximal Voluntary Isometric Contraction. After a participant's position, EMG recording, and force recordings were appropriately established, he or she performed at least three maximal voluntary isometric contractions (MVICs), 3-5 seconds in duration, with at least 60 seconds rest between attempts to prevent muscular fatigue for the purposes of determining force targets and normalizing EMG. Participants were provided with real-time visual force feedback, verbal encouragement from the investigator, and were asked if a maximal effort was made after each trial. Attempts to obtain MVIC ceased when the maximum magnitude of force produced in any two efforts was within 5% of each other and the participant agreed that maximal effort was provided. The highest MVIC force magnitude was used to calculate submaximal force targets for the elbow flexors and ankle dorsiflexors. The highest MVIC EMG magnitude of the agonist muscle was used to normalize subsequent recordings.

Submaximal Isometric Force Steadiness. Each subject performed two submaximal steadiness trials, 15-seconds in length at 2.5%, 5%, 15%, 30%, and 45% of the MVIC for elbow flexion and ankle dorsiflexion. The order of presentation of force targets was randomized. Participants completed at least one, but not more than three practice trials immediately preceding the trials used in the analysis. Individual steadiness trials at the

same target force were separated by at least 20 seconds rest. Sets of trial at different force tasks were separated by at least 60 seconds. An additional MVIC was performed upon completion of the final force target to verify absence of muscular fatigue. (Figure 2.3)

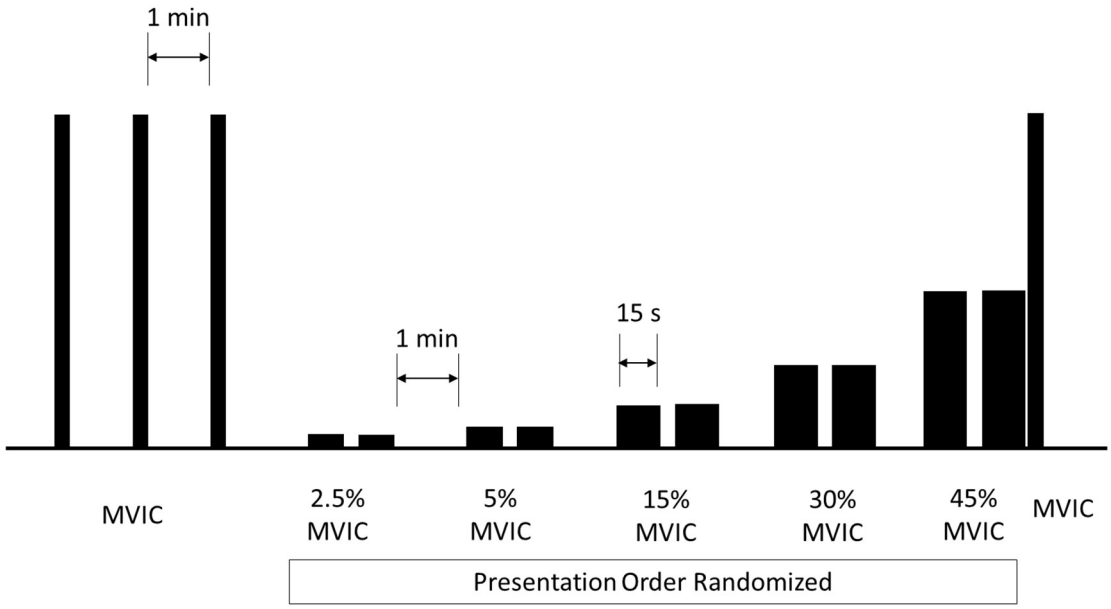


Figure 2.3 Experimental Protocol. At least three maximum voluntary isometric contractions of the elbow flexors and ankle dorsiflexors were performed to normalize EMG and calculate target force for submaximal force steadiness trials. Each participant performed 1-3 practice trials (not shown) and two trials used for analysis at 2.5, 5, 15, 30, and 45% MVIC. The order in which target forces were presented was randomized. Each trial consisted of a 15-second hold. Subsequent trials at the same target force were separated by at least 20 seconds of rest. A rest of at least 60 seconds was provided between force targets.

During steadiness tasks, participants viewed a monitor that displayed real-time force feedback over a 15-second interval with force magnitude on the y-axis and time on the x-axis. Target force was displayed as a horizontal black line that extended across the screen. Force feedback was displayed as a slightly thicker, green line that moved in the direction of the contraction. Participants were instructed to move the force tracing to the target line as quickly as possible. Once target force was attained, participants were told to

maintain the position being “as accurate and steady as possible.” During practice trials, participants were cued to “cover the black (target) line with the green (force feedback) line.” Instructions were repeated prior to each trial, but cueing, encouragement, and feedback from the investigator were not provided during the steadiness tasks included for analysis.

Cueing was not provided during these tasks for two reasons. First, the timeframe of the contraction (15 s) was short enough for participants to adequately attend to the task without a need for redirection. Second, a secondary aim of this study was to further refine methods for the second experiment in which participants simultaneously performed a cognitive task while maintaining a steady contraction. Additional cueing could complicate that task by requiring participants to attend to visual force feedback, auditory presentation of the cognitive task, and verbal instructions from the investigator. Thus, it was desirable to obtain a measure of steadiness in this experiment using the same mode of feedback.

Data Analysis

Measures of Force. Voltage recordings for force were converted to Newtons (N) using equations from calibration curves created prior to enrolling participants in the study. Torque was calculated as the product of force and length of the bony lever and expressed in Newton meters (Nm). The distance of the ankle lever was measured between the center of the ankle joint and just proximal to the metatarsal heads where the

stabilizing straps were placed. Elbow distance was measured between the olecranon process and just proximal to the radial head, the location at which the custom orthosis was attached to the force transducer setup.

MVIC force was quantified as the mean value of a 0.5 second interval centered on the peak force. Force steadiness was quantified using a 5.0 second interval centered about the midpoint of the duration of the steady hold. Steadiness was quantified in both absolute and relative measures. The standard deviation (SD) of torque was the absolute measure. The coefficient of variation (CV) was the relative measure. CV was calculated by dividing the SD by the mean (CV% = SD/mean force x 100%).

Electromyography. EMG signals were quantified using the same intervals described for collection of force data. MVIC EMG was calculated as the root mean square (RMS) over the 0.5 second interval in which the MVIC was performed. RMS values were also used to quantify muscle activity for each submaximal contraction over the 5.0 second interval selected for analysis. EMG values of all contractions were normalized to the MVIC effort with the greatest magnitude of activity. Coactivation ratios were calculated for all segments using the average normalized, RMS values of EMG (Coactivation % = agonist EMG/antagonist EMG x 100%) (Pereira et al., 2015; Rudroff, Justice, Matthews, Zuo, & Enoka, 2010).

Statistical Analysis

Data were analyzed using IBM Statistical Package for Social Sciences, Version 26 and an online effect size calculator (Ellis, 2009). Alpha was set at .05. Data are reported at mean and standard deviation, $\overline{X}$ (SD), in the text and mean and standard error

of the mean , $\bar{X}$ (SE), in figures. Variability of distributions for all variables was checked with Levene's Test for Equality of Variance for comparison of two samples and Mauchly's Test of Sphericity with three or more samples. When sphericity was violated with an epsilon value of .75 or greater, the Huynh-Feldt correction was applied. When sphericity was violated with an epsilon value below .75, the Greenhouse-Geiser correction was applied. As the sample sizes were small, effect sizes were calculated using Hedges'g when standard deviations were similar between groups and Glass' Δ when Levene's test revealed differences in variance between groups (Lakens, 2013). Effect sizes for pairwise comparisons made with the Mann Whitney U test are reported as r^2. These nonparametric effect sizes were calculated in Excel, first by determining the value of r ($r = \frac{z}{\sqrt{n}}$), then squaring the value (r^2).

Participant characteristics were compared between groups using independent t-test and Mann-Whitney U for ordinal data. Analysis of variance (ANOVA) with repeated measures on within subjects factors were used to analyze force steadiness data. The between-group factor was disease status (MS, control). The within subjects factors were muscle group (elbow flexors, ankle dorsiflexors) and load (2.5, 5, 15, 30, and 50% MVIC). When the F-statistic was significant, post hoc comparisons were made using independent t-tests to examine differences at each force target between groups.

Pearson's product moment correlations (r) between ankle and elbow steadiness were compared within groups. Associations among other measures was examined with Pearson's r for interval and ratio data and Spearman's rank correlation coefficient for ordinal data.

RESULTS

Participant Characteristics. Participant characteristics are reported in Table 2.1. The MS and control groups were similar in age, height, and body mass. People with MS had greater levels of depression (CESD) score, greater fatigue (MFIS), lower scores for activity-based measures (25FWT and 9HPT), lower cognitive measures (PASAT-3) and weaker ankle dorsiflexors (ankle dorsiflexion MVIC).

Table 2.1: Participant Characteristics.

Variable	MS (n=15; 5 male)	Control (n=15; 3 male)	*p*	*Effect size*
Age, yr	49.67 (9.47)	47.20 (6.42)	.411	
Height, cm	168.62 (6.77)	168.63 (10.74)	.998	
Mass, kg	80.21 (16.67)	80.18 (16.79)	.996	
BMI, kg/m^2	28.32 (5.63)	28.07 (4.51)	.933	
CESD	10.27 (5.65)	3.93 (4.06)	.001 *	0.36†
MFIS Total	35.60 (13.11)	8.73 (10.97)	.000 *	0.57†
MFIS Physical	14.53 (7.25)	2.93 (5.22)	.000 *	0.52†
MFIS Cognitive	18.21 (5.02)	5.40 (5.66)	.000 *	0.56†
MFIS Psychosocial	2.87 (2.26)	0.40 (0.74)	.000 *	0.39†
25FWT, s	4.99 (1.20)	3.78 (0.46)	.002 *	1.30
9HPT, s	21.50 (0.36)	17.82 (1.39)	.000 *	2.65
PASAT-3, n	44.47 (11.75)	54.60 (5.30)	.007 *	1.08
Ankle dorsiflexion MVIC, Nm	7.16 (2.49)	15.15 (5.19)	.000 *	1.54
Elbow flexion MVIC, Nm	45.19 (14.16)	43.29 (16.88)	.740	

Note: Values are mean (SD); * $p < .05$; Effect sizes are Hedge's g or r^2 (†).
BMI = Body mass index, CESD = Center for Epidemiologic Studies Depression Scale, MFIS = Modified Fatigue Impact Scale, 25FWT = 25-foot Walk Test, 9HPT = 9-hole Peg Test, PASAT-3 = Paced Auditory Serial Addition Test, 3 second interval, MVIC = Maximum voluntary isometric contraction

MS-specific characteristics are reported in Table 2.2. The MSFC incorporates the 25FWT, 9HPT, and PASAT-3. It is expressed as a z-score in relation to the population with MS with higher scores indicating better function. Thus, our sample's mean score of 0.22 indicates slightly better function than the population. The mean score of 0.93 on the

PDDS, a self-reported measure of MS-related disability, indicates that our sample perceived themselves as having normal function to mild disability.

Table 2.2: MS-Specific Participant Characteristics.

Variable	MS (n=15; 5 male)
MS Duration, months	158.73 (112.76)
MSFC	0.22 (0.39)
PDDS	.93 (1.33)
FAMS Total	165.20 (25.66)
FAMS Mobility	18.33 (2.64)
FAMS Symptoms	23.03 (3.67)
FAMS Emotional Well-Being	23.00 (3.02)
FAMS General Contentment	21.20 (4.26)
FAMS Thinking and Fatigue	18.47 (5.01)
FAMS Family/Social Well-Being	21.67 (5.83)
FAMS Additional Concerns	39.33 (7.81)

Note: Values are mean (SD) MSFC = Multiple Sclerosis Functional Composite, PDDS = Patient Determined Disease Steps, FAMS = Functional Assessment of Multiple Sclerosis

Force Steadiness: Ankle. Ankle dorsiflexion MVIC was weaker in people with MS (Figure 2.4) and the resulting target forces consequentially lower. The absolute measure of force fluctuation, SD, was not different between groups at any force level [$F(1.01, 28.38) = 2.96$, $p = .096$]. The relative measure of force fluctuation, CV, was greater in those with MS for all force target levels except 15% MVIC [$t(27.43) = -1.72$, $p = .097$]. Figure 2.5 illustrates the absolute and relative force steadiness for both samples across all forces. Effect sizes for force differences ranged from 0.61 to 1.21; 2.5% [$t(17.10) = -3.20$, $p = .005$, $\Delta = 0.87$], 5% [$t(16.76) = -4.02$, $p = .001$, $\Delta = 1.09$], 30%

[t(28) = -3.40 , p = .002 , g = 1.21], and 45% [t(21.62) = -2.09 , p = .049 , Δ = 0.61]. See Table 2.3 for descriptive statistics of ankle and elbow force fluctuation.

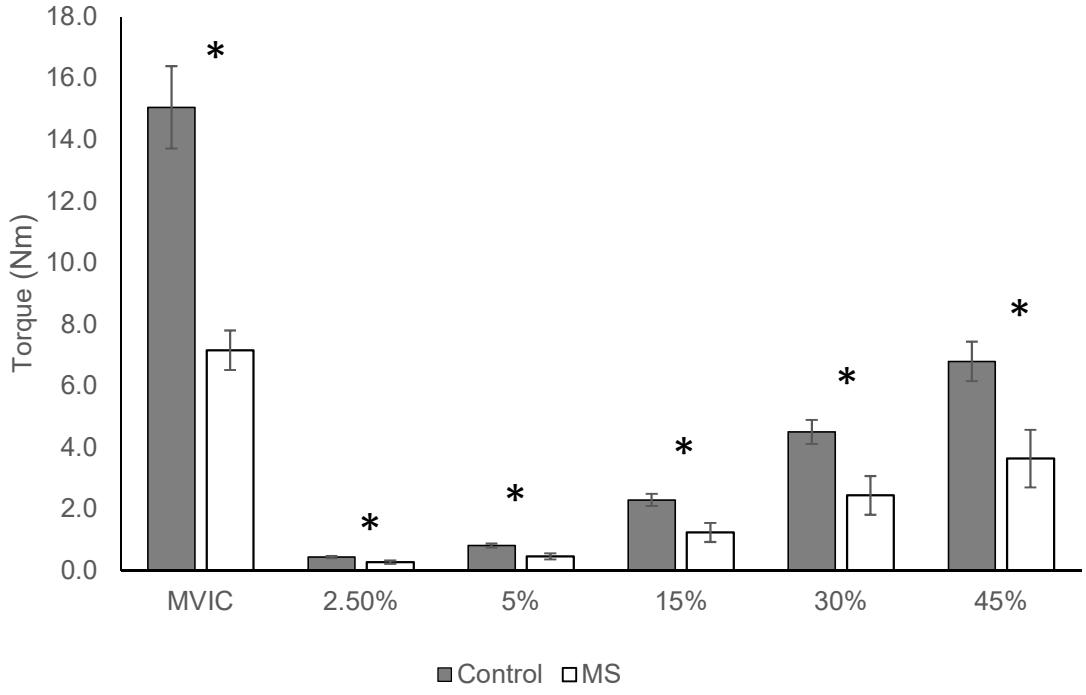


Figure 2.4. Ankle MVIC and Target Torques. Mean (SE) for MVIC and submaximal torque for controls (closed) and those with MS. Controls produced more torque than those with MS in the MVIC and at all submaximal force targets, * $p < .05$

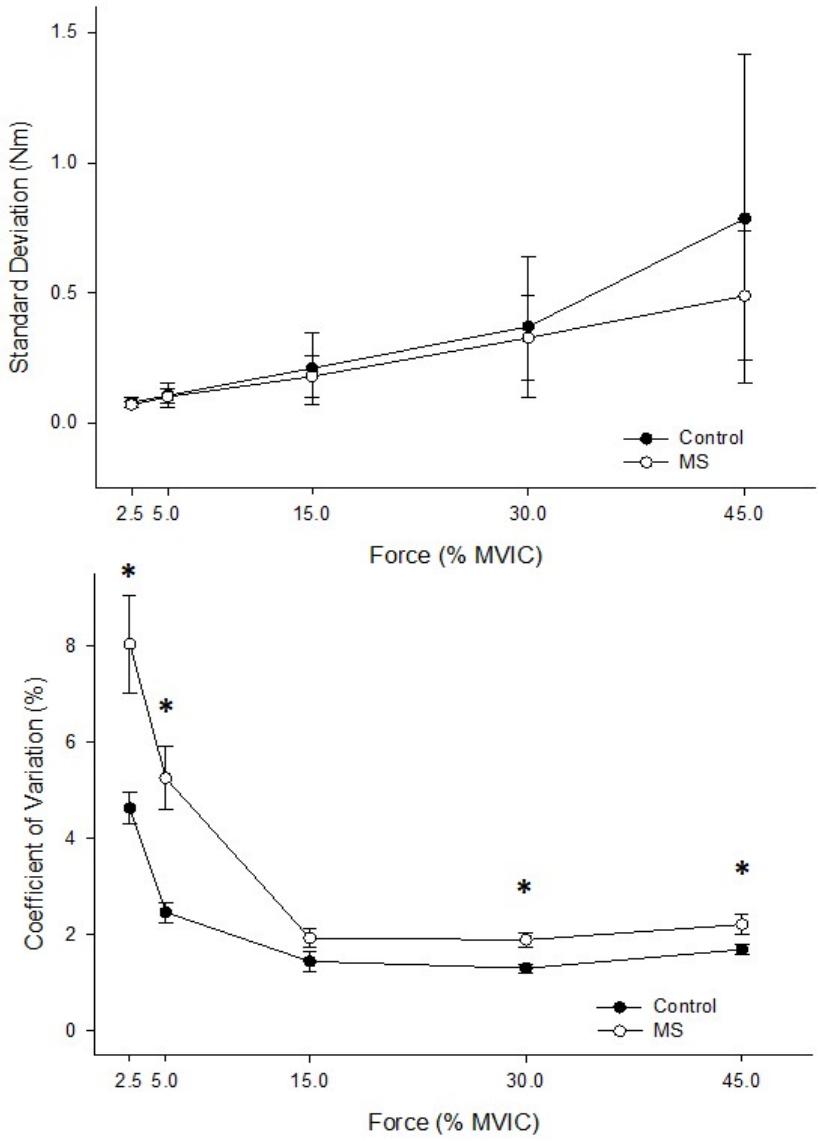


Figure 2.5. Relative and Absolute Ankle Steadiness. (A.) Standard deviation (SD) of torque across the range of submaximal target forces. MS (open) and controls (closed) did not differ in absolute magnitude of force fluctuation. (B.) Coefficient of variation (CV) across the range of submaximal target forces. Between group CV differed for all force targets except 15% MVIC. (* $p < .05$)

Force Steadiness: Elbow. MVIC and submaximal torque generated by the elbow flexors did not differ between groups for MVIC or any force target (Figure 2.6); MVIC [$t(28) = -.34$, $p = .740$], 2.5% [$t(28) = -.16$, $p = .847$], 5% [$t(28) = -.50$, $p = .625$], 15% [t

(28) = -.53, p = .602], 30% [t (28) = -.438, p = .665], and 45% [t (28) = -.21, p = .839]. Absolute force fluctuation, SD, was greater in those with MS at the 2.5% target [t(14) = -2.15, p = .050, g = 0.81], but not at higher targets [t (14.00) = -.2.02, p = .063], 15% [t (14.02) = -2.07, p = .058], 30% [t (14.11) = -1.58, p = .137], and 45% [t (14.17) = -1.49, p = .159]. Relative fluctuation, CV, was higher for the MS sample at lower force targets of 2.5 and 5% [2.5% t(28) = -2.35, p = .026, g = 0.84; 5% t(28) = -2.12 , p = .043, g = 0.75]. CV did not differ between groups at higher force targets of 15%, 30%, and 45% MVIC; 15% [t (17.53) = -2.06, p = .054], 30% [t (28) = -.99, p = .329], and 45% [t (28) = -.347, p = .731]. Figure 2.7 illustrates the absolute and relative force steadiness for both samples across all forces. Additionally, the standard deviation of the absolute and relative fluctuation, SD and CV respectively, were larger in people with MS. See Table 2.3 for descriptive statistics of ankle and elbow force fluctuation.

Table 2.3: Force Fluctuation Values for Ankle Dorsiflexors and Elbow Flexors

Ankle Dorsiflexors		2.5% MVIC	5% MVIC	15% MVIC	30% MVIC	45% MVIC
Control	SD	.078 (.080)	.106 (.181)	.210 (.533)	.370 (1.048)	.786 (2.441)
	CV	4.634 (1.309)	2.465 (.808)	1.443 (.828)	1.304 (.351)	1.694 (.460)
MS	SD	.069 (.043)	.101 (.108)	.178 (.313)	.327 (.632)	.488 (.966)
	CV	8.040 (3.90)	5.252 (2.560)	1.930 (.716)	1.893 (.572)	2.213 (.846)
Elbow Flexors		2.5% MVIC	5% MVIC	15% MVIC	30% MVIC	45% MVIC
Control	SD	.016 (.010)	.023 (.009)	.075 (.051)	.294 (.216)	.592 (.383)
	CV	3.908 (1.717)	2.982 (1.474)	1.779 (.581)	2.351 (1.080)	3.004 (1.215)
MS	SD	.348 (.599)	.637 (1.177)	1.160 (2.035)	1.707 (3.460)	2.942 (4.929)
	CV	5.643 (2.282)	4.279 (1.863)	2.696 (1.622)	2.769 (1.219)	3.182 (1.562)

Values expressed as mean (SD).

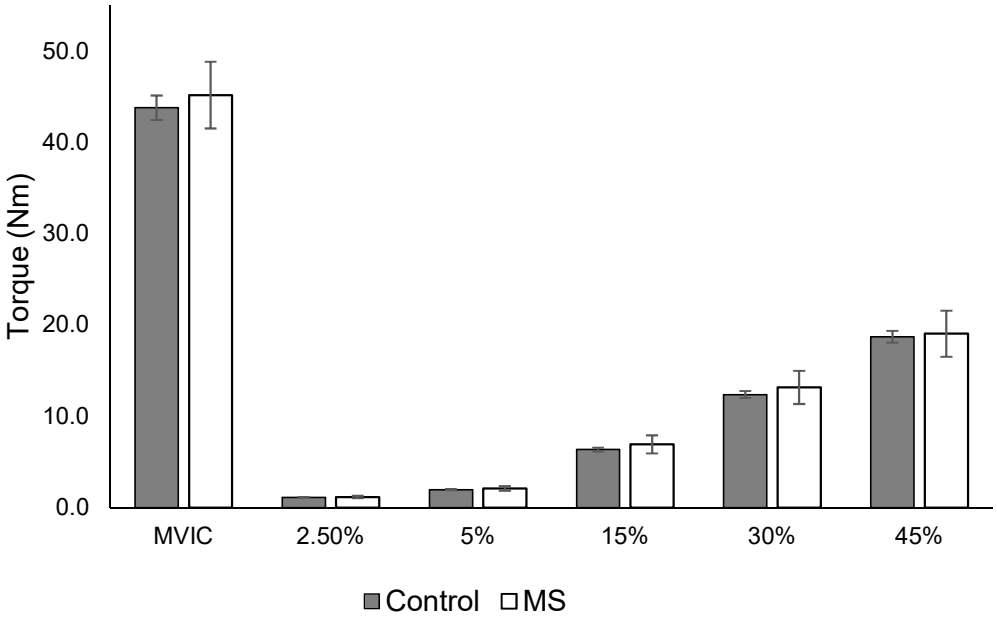


Figure 2.6. Elbow MVIC and Target Torques. Mean (SE) for MVIC and submaximal torque for controls (closed) and those with MS. Groups produced similar torque at all targets.

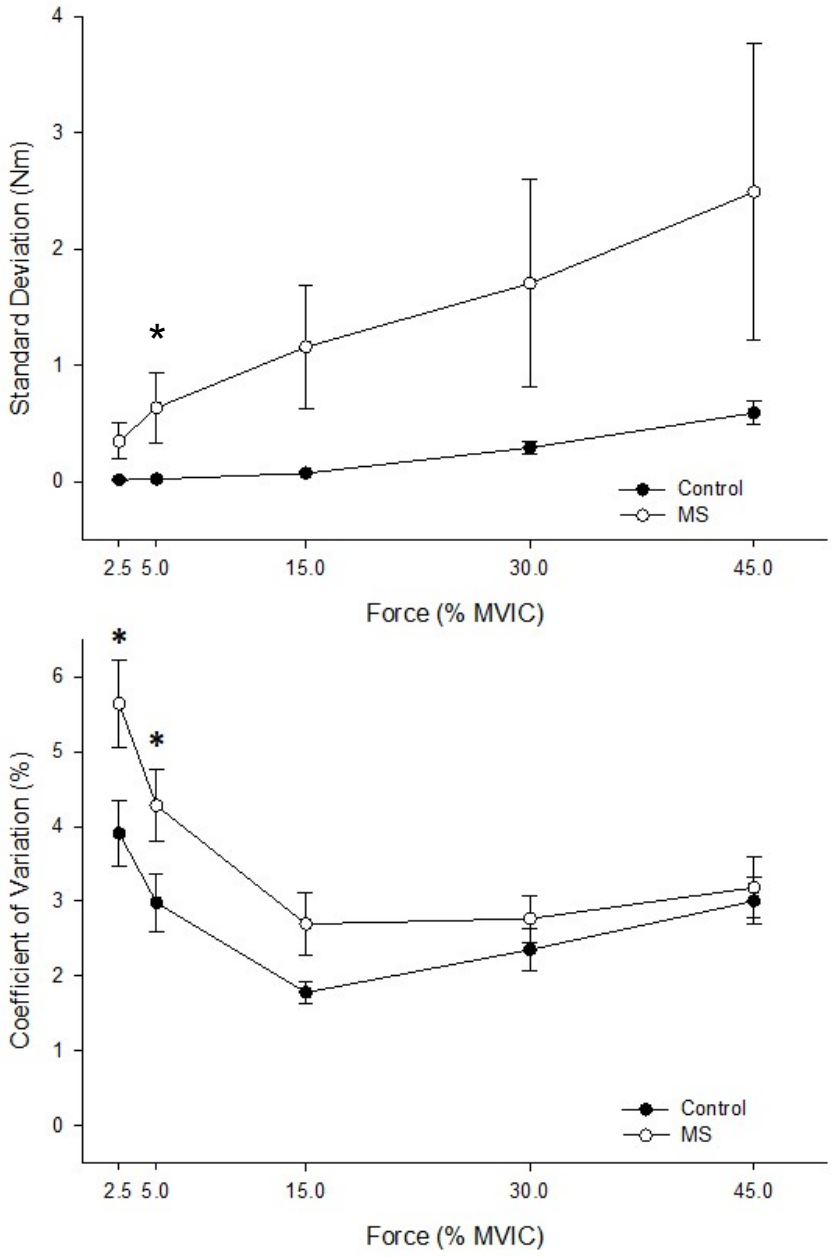


Figure 2.7. Relative and Absolute Elbow Steadiness. (A.) Standard deviation (SD) of torque across the range of submaximal target forces. MS (open) and controls (closed) did not differ in absolute magnitude of force fluctuation. (B.) Coefficient of variation (CV) across the range of submaximal target forces. Between group CV differed for 2.5 and 5%

Force Steadiness Associations. Associations of force steadiness in the elbow flexors and ankle dorsiflexors were explored within groups. No significant associations in relative fluctuation were found between upper and lower extremities in either group at any force as illustrated in Figure 2.8. Furthermore, there were few significant correlations between CV and MVIC. In controls, ankle MVIC and CV were strongly associated at the 2.5% target [r(13) = - 0.75, p = .001] and moderately associated in the elbow at 2.5% [r(13) = - 0.52, p = .049], 5% [r(13) = - 0.54, p = .037], and 15% MVIC [r(13) = - 0.55, p = .034]. In those with MS, there was a moderate correlation at the elbow for at the 2.5% MVIC target [r(13) = - .62, p = .013]. Thus, in our sample, weaker maximal contractions (MVIC) were associated with greater force fluctuation (CV) values at very low forces in the elbow flexors of both groups and in the ankle dorsiflexors of controls.

Muscle Activation. An attempt was made to calculate muscle coactivation for the ankle (tibialis anterior and medial gastrocnemius) and elbow (biceps brachii and triceps brachii) by dividing the normalized magnitude of the agonist EMG by the antagonist. In both sample and both muscle groups, coactivation could not be calculated due to inadequate signal-to-noise ratio in the antagonist muscles.

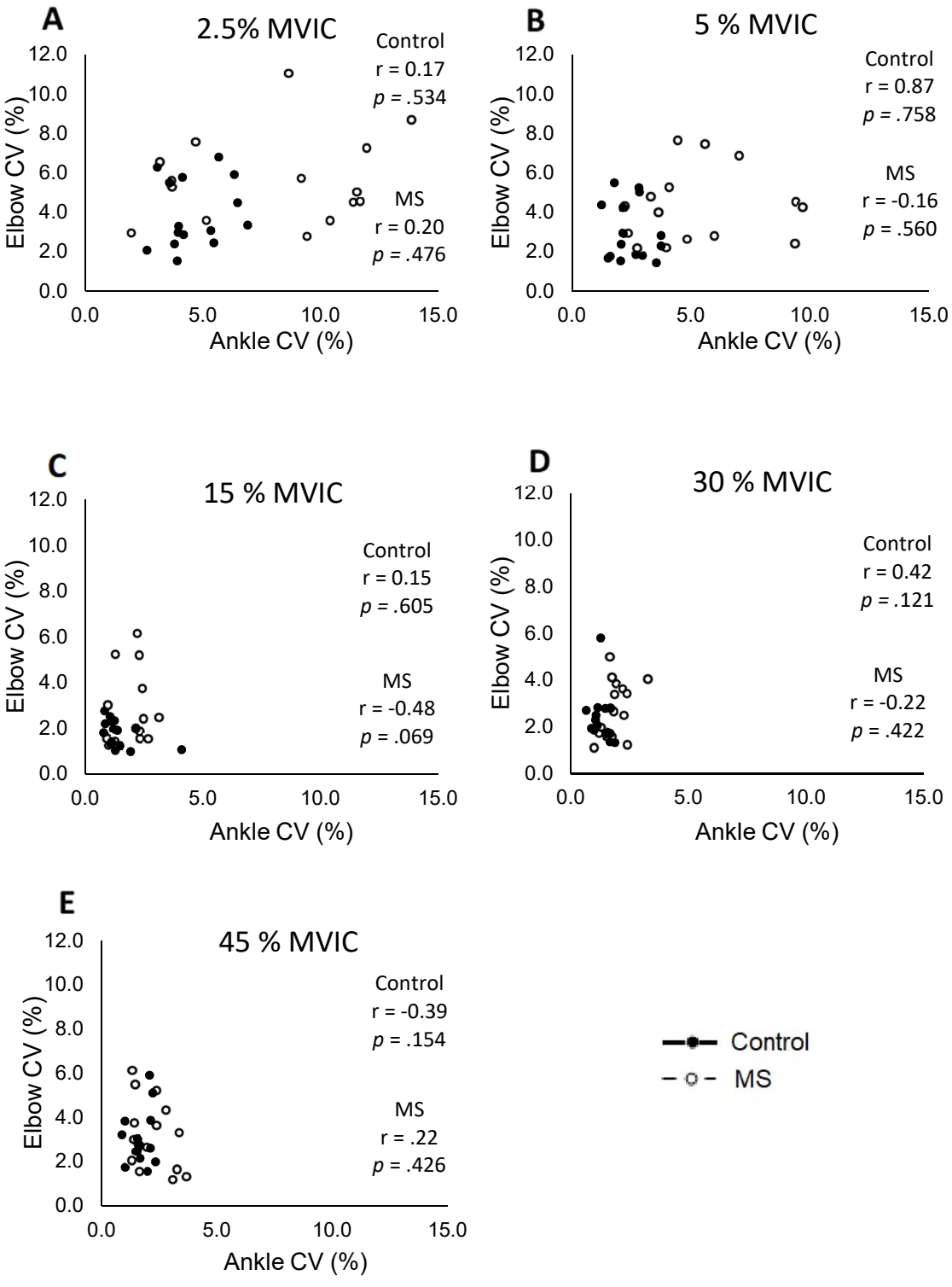


Figure 2.8. Associations of Steadiness in Upper and Lower Extremities. Pearson product moment correlations (r) were not significant within either group at any force target, A. 2.5%, B. 5%, C 15%, D 30%, and E 45%.

Salient Associations. There were no significant within group associations between elbow CV and ankle CV at any force level in either people with MS or controls as shown in Figure 2.8. There were no significant associations between tibialis anterior CV at any force level and the measures that were different between groups, the CESD [Ankle Controls: 2.5% r_s (13) = .10, p = .727; 5% r_s (13) = -.01, p = .979; 15% r_s (13) = .04, p = .897; 30% r_s (13) = .03, p = .918, 45% r_s (13) = .04, p = .887 and MS: 2.5% r_s (13) = .30, p = .272; 5% r_s (13) = .17, p = .557; 15% r_s (13) = .20, p = .485; 30% r_s (13) = -.13, p = .643, 45% r_s (13) = .02, p = .954] and MFIS total score [Controls: 2.5% r_s (13) = -.05, p = .849; 5% r_s (13) = -.13, p = 0.646; 15% r_s (13) = -.07, p = .799; 30% r_s (13) = -.03, p = .929, 45% r_s (13) = .06, p = .839 and MS: 2.5% r_s (13) = .11, p = .685; 5% r_s (13) = .16, p = .576; 15% r_s (13) = .11, p = .704; 30% r_s (13) = .01, p = .960, 45% r_s (13) = .104, p = .960] Additionally, for the elbow flexors there were no within group correlations with either the CESD [Controls: 2.5% r_s (13) = -.48, p = .071; 5% r_s (13) = -.42, p = .116; 15% r_s (13) = -.36, p = .186; 30% r_s (13) = -.413, p = .127, 45% r_s (13) = .41, p = .510 and MS: 2.5% r_s (13) = -.23, p = .403; 5% r_s (13) = .03 , p = .929; 15% r_s (13) = .05, p = .854; 30% r_s (13) = .34, p = .222, 45% r_s (13) = .27, p = .339] or MFIS [Controls: 2.5% r_s (13) = -.44, p = .099; 5% r_s (13) = -.30, p = .274; 15% r_s (13) = -.09, p = .740; 30% r_s (13) = -.22, p = .424, 45% r_s (13) = -.421, p = .118 and MS: 2.5% r_s (13) = -.13, p = .657; 5% r_s (13) = .239, p = .390; 15% r_s (13) = .15, p = .594; 30% r_s (13) = -.04, p = .879, 45% r_s (13) = -.05, p = .850]. Because the control and MS group differed in ankle MVIC, but not elbow MVIC, the association between CV of all force targets and MVIC of the ankle was tested and found to be insignificant in both controls and those with MS with the exception of 2.5% MVIC in controls [Controls: 2.5% r (13) = .746 , p = .001; 5% r (13) =

-.43, p = .112; 15% r (13) = -.12, p = .668; 30% r (13) = .01, p = .967, 45% r (13) = -.36, p = .183 and MS: 2.5% r (13) = -.31, p = .264; 5% r (13) = -.19, p = .509; 15% r (13) = -.48, p = .069; 30% r (13) = -.25, p = .373, 45% r (13) = -.08, p = .788]

Moderate relations between ankle CV and 25FWT were significant for all target forces except 30% MVIC [2.5% r (13) = .68, p = .005; 5% r (13) = .61, p = .015; 15% r (13) = .57, p = .026; 30% r (13) = .49, p =.065; and 45% r (13) = -.64, p = .008)]. However, these associations were not observed in those with MS [2.5% r (13) = -.11, p = .701; 5% r (13) = -.07, p = .807; 15% r (13) = -.39, p = .154; 30% r (13) = -.383, p =.158; and 45% r (13) = -.22, p = .429)]. Associations between the 9HPT and CV of the elbow at any force for either group were not significant with the exception of a moderate correlation at 30% MVIC in the group with MS [Controls: 2.5% r (13) = -.17, p = .557; 5% r (13) = -.05, p = .830; 15% r (13) = -.05, p = .867; 30% r (13) = .40, p = .138, 45% r (13) = .27, p = .338 and MS: 2.5% r (13) = -.25, p = .363; 5% r (13) = -.25, p = .375; 15% r (13) = -.35, p = .202; 30% r (13) = -.57, p = .026, 45% r (13) = -.44, p = .098].

DISCUSSION

This study is the first to explore non-fatiguing submaximal isometric force steadiness across a range of forces in joints of the upper and lower extremities in people with MS. A novel finding is that the observed pattern of force fluctuation is consistent with the literature examining steadiness of the same muscle groups in healthy populations of young and old adults (Jesunathadas et al., 2012; Taylor, Christou, & Enoka, 2003; Tracy et al., 2005; Yoon et al., 2014). In both controls and those with MS, absolute

fluctuation (SD) was lowest at the lowest target force and highest at the highest target force. Relative fluctuation (CV) was highest at very low forces (2.5 and 5% MVIC) and lowest at low-effort contractions (15% MVIC).

The first purpose of this study was to compare force steadiness during low-force, non-fatiguing isometric contractions between people with MS and healthy controls. It was hypothesized that those with MS would be less steady than controls in both joints at all force levels. This hypothesis was influenced by findings of Arpin (2016) and Davies (2015) who observed that people with MS were less steady than healthy controls for isometric steadiness tasks of the ankle plantar flexors at 20% MVIC. Our findings were consistent with these reports in that controls were steadier at all ankle forces except 15% MVIC. These differences in relative ankle force fluctuation were associated with large effect sizes.

Comparisons of elbow fluctuation between groups were not identical to our findings in the ankle. Unlike the ankle in which differences in CV were observed at higher and very low force targets, elbow CV only differed in people with MS at very low forces (2.5 and 5% MVIC). We did not observe the same phenomenon in the elbow flexors. In the elbow, those with MS were less steady than controls only at very low force targets of 2.5% and 5%. Even though the groups did not differ in strength and steadiness at and above 15% MBIC, the MS sample greater variability in the CV than controls at all force levels.

Interestingly, people with MS are less steady than controls at very low forces (2.5% MVIC) in both the upper and lower extremities and the effect is moderately large to large. It is known that the dendrites of alpha motor neurons receive multiple inputs

from cortical neurons and interneurons and that these inputs can further be distributed across individual motor units in the same pool. The net effect is a shared synaptic input results in low-frequency oscillations in central drive that influences motor unit discharge rates and can contribute to force fluctuation (Negro et al., 2009; Negro et al., 2016; Pereira et al., 2019). Thus, it is reasonable to speculate that neural degeneration associated with MS could potentially influence the frequency of this underlying drive, amplifying fluctuations at the lowest forces in which steadiness is particularly sensitive to changes in common synaptic input. This could explain the group differences and large effect sizes observed only at low forces. This could be explored by repeating our experimental tasks while recording discharge rates of single motor units using intramuscular EMG.

The second purpose of this study was to determine if people with MS used a different motor control strategy than healthy controls. It was hypothesized that people with MS may use a co-contraction strategy to improve steadiness. In both upper and lower limbs of controls and those with MS, antagonist muscle EMG did not exceed the threshold for noise in any trial. Our 2-channel surface EMG measurement was lacked sensitivity to adequately measure motor unit discharge rates and provide insight into the mechanisms underlying motor control. However, it does show that, contrary to our hypothesis, people with MS did not use a different pattern of activation to complete the experimental tasks as both groups had antagonist EMG values near the threshold for noise.

The third purpose was to compare force steadiness between upper and lower extremity muscles in the same group of individuals. It was hypothesized that the CV of

force would positively correlate between the elbow and ankle at all force targets within groups. However, no significant correlations were observed. This could be due to differences in corticospinal projections between upper and lower extremity neurons. In our experiment the elbow force was produced primarily by the biceps brachii. However, the effects of the agonist brachioradialis could not be controlled. Similarly, it is likely that the tibialis anterior, extensor digitorum, and extensor hallucis all contributed to dorsiflexion. The cortical representation of the upper limb muscles we examined is larger than the lower limb muscles used. Thus, one could speculate that control of additional pyramidal neurons could pose a greater demand on executing motor commands. Examination of the cortical map for each of these regions using fMRI could provide further insight.

Experience is another possible explanation for the finding that people with MS were less steady than controls for ankle forces at or above 15% MVIC, but just as steady in the elbow forces at these same force targets. For example, the upper extremity is involved in reaching and grasping tasks in which visual location of a target is the first step in the process. While the hand is being transported to the target, both somatosensory and visual feedback are used to refine the movement. Because visual feedback was the mode by which our participants made determinations about force adjustments, it is possible that experience allowed them to more easily use our visual feedback when controlling the arm. Our participants with MS had the disease for an average of 159 months, providing many opportunities to gradually accommodate for losses in motor control through normal daily activities involving reaching and grasping. It is reasonable to speculate that any positive practice effects may have been adequate to manage

impairments at higher force targets, but not at lower targets at which the effects of synaptic noise and common inputs to the motor unit pools are more robust.

It is also possible the structure of the muscle itself could be responsible for the differences in association of CV between muscle groups. A definitive reference indicating a precise range of the number in whole muscles are lacking. However, studies that have explored this concept report a greater number of motor units in the biceps brachii than in the tibialis anterior (A. Hamilton et al., 2004; McComas, 1998). If each motor unit is considered a degree of freedom that can be controlled, it suggests that demands on cortical resources may be different and could account for our observation.

An association between ankle CV and the 25FWT was observed in controls, but not in those with MS. Moderate, positive correlations were discovered at all but the 30% force target. There was a moderate relation at this target force that approached significance suggesting that our design had inadequate power to reveal this secondary finding. This contrasts with the MS group that did not approach significant associations between the 25FWT time and CV at any force level. This further suggests that the mechanisms underlying force isometric force steadiness may also contribute to the dynamic activity of gait. This observation is consistent with Davies and colleagues (2015) who found that a neurorehabilitation program not only improved submaximal isometric force steadiness of the ankle plantar flexors, but that these improvements occurred in conjunction with functional improvements in postural control and ambulation.

Collectively, these findings suggest that people with multiple sclerosis have impairments of force steadiness at lower forces and that there may a functional significance for gait when ankle steadiness is compromised.

CHAPTER 3: DUAL COGNITIVE-MOTOR TASK PERFORMANCES IN PEOPLE WITH MULTIPLE SCLEROSIS

INTRODUCTION

Typical activities rarely require that people sequentially perform tasks one at a time. Instead, activities of daily living often require simultaneous performance of two or more tasks such as maintaining stable standing while completing a retail transaction or carrying on a conversation while walking. Because attention is a limited resource (Baddeley, 1983; Kahneman, 1973) and is required to complete each task, it is logical to surmise that simultaneous performance of two tasks results in decreased performance in both tasks. This DTE can be quantified for both the motor and cognitive performances by comparing the same outcome under single and dual task conditions (Plummer & Eskes, 2015; Plummer et al., 2014).

People with MS are known to experience both motor and cognitive impairments (Amato et al., 2006; Cameron & Nilsagard, 2018; Chiaravalloti & DeLuca, 2008; Compston & Coles, 2008; Filippi et al., 2018; Noseworthy et al., 2000; Olek, 2005; Rao et al., 1991; Thompson, Baranzini, et al., 2018; Widener, 2007). As such, it is important to understand dual task performance in this population to assist in developing effective rehabilitation interventions. Dual task studies of people with MS have frequently involved ambulation tasks (Hamilton et al., 2009; Kalron et al., 2010; Learmonth et al., 2015; Mofateh et al., 2017; Nogueira et al., 2013; Pau et al., 2018; Saleh et al., 2018; Sandroff, Benedict, et al., 2015), leaving static, submaximal postural control tasks unexplored. The purpose of this experiment was to examine dual task effects of a cognitive motor task in people with MS. The motor task was maintaining force steadiness

during a non-fatiguing, submaximal isometric contraction. The cognitive task was performing two variations of the Paced Auditory Serial Addition Test (PASAT) (Gronwall, 1977) in which participants provided the sum of single digit number presented at a specific rate. In one variation, digits were presented at 3-second intervals (PASAT-3) and in the other, digits were presented at 4-second intervals (PASAT-4).

Because PASAT performance is influenced by processing speed (Chiaravalloti et al., 2013; Fisk & Archibald, 2001), we hypothesized that all participants would experience a negative DTE on cognition with the addition of a motor task consisting of a steady, isometric contraction and that this effect would be greater in the PASAT-3 condition than in the PASAT-4. We hypothesized that cognitive dual task effects would be greater in those with MS. We also hypothesized similar negative dual task effects on motor performance using coefficient of variation (CV) of force fluctuation as the motor outcome of interest. It was hypothesized that all participants would experience a negative motor DTE with addition of a cognitive task, the effect would be greater when performing the PASAT-3 task than the PASAT-4 task, and the effect would be greater in those with MS.

METHODS

Thirteen people with MS (2 males and 11 females; mean (SD): 48.2 (10.2) years; 166.0 (7.6) cm height, 77.0 (12.8) kg body mass) and thirteen healthy controls (1 male and 12 females; mean (SD): 46.5 (5.5) years; 168.0 (84.1) cm in height, 84.1(16.6) kg in body mass) volunteered to participate in the study. Volunteers were eligible to participate

if they were between the ages of 18 and 60 and could actively dorsiflex the left ankle through a full range of motion against gravity. Volunteers with MS were eligible if disease progression was stable for at least six months. Participants were excluded if they lacked sufficient visual acuity to see a computer monitor at a distance of 1.0 meter or experienced any condition other than MS that impaired normal function of the left ankle.

The experiment was conducted in a single session at Marquette University. In addition to completing experimental procedures, volunteers were oriented to the protocol and provided informed consent as approved by the university's Institutional Review Board (Protocol HR-1803022784).

Participants

Recruitment and Enrollment. Participants were recruited and consecutively enrolled in the study as described in Chapter 2.

Participant Characteristics. All participants completed surveys of depression, primary fatigue, and general health using the Centers for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977), Modified Fatigue Impact Scale (MFIS) (Rivito et al., 1997), and Patient-Reported Outcomes Measurement Information System (PROMIS) Global Well Being instrument (Hays, Bjorner, Revicki, Spritzer, & Cella, 2009), respectively. Participants with MS also completed measures of disability and quality of life using the Patient Determined Disease Steps Scale (PDDS) (Learmonth, Motl, et al., 2013; Rizzo et al., 2004) and the Functional Assessment of Multiple Sclerosis (FAMS) (Cella et al., 1996), respectively.

Each participant provided his or her age, birth month, birth year, biologic sex, and number of years of secondary and postsecondary education completed. Participants with multiple sclerosis also provided the month and year of diagnosis, disease subtype, and the names of disease modifying medications used at the time the experiment took place. Height was measured with a stadiometer and weight measured with a digital scale.

Multiple Sclerosis Functional Composite (MSFC). All participants completed tasks of the MSFC as described in Chapter 2. These tasks included a 9-hole peg test (9HPT), 25-foot walk test (25FWT), and Paced Auditory Serial Addition Test with a total of 60 stimuli presented every three seconds (PASAT-3). MSFC composite scores were calculated for participants with MS by converting individual measures to z-scores and comparing to population estimates of those with MS published in the MSFC guidebook.

Cognitive Tasks

Symbol Digit Modalities Test. All participants completed the Symbol Digit Modalities Test (SDMT) (Western Psychological Services, Torrance, CA). The SDMT is considered to be a measure of cognitive processing speed and is a reliable, valid measure of cognition in people with MS (Benedict et al., 2017; Strober et al., 2018; Van Schependom et al., 2014).

The SDMT was administered by presenting participants with a worksheet with a header consisting of a key for matching nine single digit numbers (1-9) to nine distinct symbols. The body of the worksheet contained rows of symbols. Participants were asked to identify the digit that corresponded to each symbol. The first ten symbols were practice

items and completed with guidance from the investigator. Upon completion of the practice items, participants vebalized as many responses as possible in 90 seconds.

Standard administration of the SDMT includes two presentations of the task. In the first, participants write responses on the worksheet. In the second, participants verbalize responses. To minimize a learning effect and diminish potential effects of sensory or motor impairments in participants with MS, only the second condition (spoken responses) was performed in this study.

Serial 3 and Serial 7 Participants were instructed to count backward for 30 seconds starting with a three-digit inter. The starting integer was obtained from a random number generator (M. Haahr, 2019). An attentional control task, counting backward by one, was performed first. The subsequent 3s and 7s tasks were presented in random order. One practice trial up to 10-seconds in length was administered prior to each scored task to ensure that participants were aware of the number to be subtracted. One one 30-second trial for each level of difficulty (1, 3, or 7) was administered. Responses were documented by the investigator and later checked for accuracy. The accuracy rate (number of correct responses / 30 s) was calculated to allow comparison the cognitive Timed Up and Go (TUGc), a clinical dual-task measure in which counting backward by 3 is done during a motor task that varies in duration.

Participants were permitted to respond by stating either the name of the integer or sequence of digits. For example, the responses *one-hundred nineteen*, *one-nineteen*, and *one-one-nine,* were considered equivalent. Participants were told to "state as many correct answers as possible in 30 seconds." Here is an example of standard instructions using the serial 7 task and the starting number 219, "When I say go, count backward by 7

starting at two-hundred nineteen. Two – one – nine. Go." In addition to verbal instructions, the examiner held up one, three, or seven fingers to emphasize the task during delivery of instructions.

Clinical Measures

All participants completed clinical measures of balance and mobility. A clinical measure of dual task effect, the cognitive Timed Up and Go (TUGc) was also performed.

Timed Up and Go (TUG). Participants completed two trials of the Timed-Up-and-Go (TUG) test (Podsiadlo & Richardson, 1991), a measure with good reliability in populations with MS (Learmonth, Paul, McFadyen, Mattison, & Miller, 2012; Nilsagard, Lundholm, Gunnarsson, & Denison, 2007). This measure of general mobility (Sebastião, Sandroff, Learmonth, & Motl, 2016) requires participants to complete a series of functional movements as rapidly as safely possible. Participants were seated in a standard chair with armrests. When the investigator gave the command, "Go," participants rose from the chair, walked three meters to a marker taped on the floor, turned, walked back to the chair, and resumed a seated position. The time (s) to complete the task was recorded. The stopwatch was started when the investigator gave the "go" command and was stopped when the participant's buttocks touched the chair. One practice trial and two recorded trials were completed. The average of the two recorded trials was used in analyses.

Cognitive Timed Up and Go (TUGc). Participants repeated the TUG while simultaneously performing a cognitive secondary task of counting backward by three.

Participants were given a randomly generated number (random.org) between 20 and 100 from which the subtraction task began. Instructions were provided as follows using the number 28 as the starting point. “When I say go I want you to repeat the task while counting backward by 3’s starting at twenty-eight. Two – eight. Go.” As with the other serial subtraction tasks, the responses were recorded and later checked for accuracy and number of responses. One practice trial and two scored trials were completed and the average of these trials reported.

Berg Balance Scale (BBS). The Berg Balance Scale, an ordinal measure of balance (Berg, Wood-Dauphinee, Williams, & Maki, 1992), was administered to all participants by an experienced physical therapist. Each participants total score was recorded and included in data analysis.

The BBS has good interrater and intrarater reliability when used in a population with MS (Cattaneo, Regola, & Meotti, 2006; Learmonth et al., 2012). Each of the 14 items on the BBS is rated using a 5-point scale with 0 being the lowest possible performance and 4 being the highest. BBS scores range between 0 and 56 points with higher scores indicating better performances. Tasks primarily address postural control, the ability to maintain the center of mass within the base of support. Most tasks involve standing while keeping the feet in a stationary position. The BBS does not assess balance while walking.

Functional Gait Assessment (FGA). The Functional Gait Assessment, a measure of balance during walking (Wrisley, Marchetti, Kuharsky, & Whitney, 2004) was administered by an experienced physical therapist. The FGA is a reliable assessment for a population with MS (Cattaneo et al., 2006; Forsberg, Andreasson, & Nilsagård, 2016).

The FGA is an ordinal-scale, activity measure of balance that requires participants to complete 10 ambulation tasks over a 6-meter walkway. Tasks include changing gait speed, turning the head, closing the eyes, walking backward, navigating obstacles, negotiating stairs, and walking with a narrow base of support. Each item is scored on a 4-point scale with a score of 0 assigned to the lowest possible performance and 3 for the highest. Total scores range from 0-30 with higher scores indicating better performances.

Experimental Setup and Measures

Measures of Force. Experimental tasks were performed using the left ankle dorsiflexors. The left ankle was secured to a footplate attached to a force transducer as described in Chapter 2. Participants wore flat-soled athletic shoes during testing. Force output was measured using a custom strain gauge transducer (Transducer Techniques, Temecula, CA), amplified X100 (Grass Telefactor, Model P122, Warwick, RI) and digitized with a Power 1401 analog to digital convertor (Cambridge Electronic Designs, Cambridge, UK) and sampled at 500 Hz with Spike 2.7 software (Cambridge Electronic Designs, Cambridge, UK) at 500 Hz as described in Chapter 2. The experimental setup for the ankle is depicted in Figure 2.2.

Real-time, continuous visual force feedback was displayed over a 15-second window on a 27” monitor placed 1-meter in front of the participant. The y-axis display remained constant across all targets as increased visual gain has been shown to positively affect force steadiness in muscles of the ankle (Prodoehl & Vaillancourt, 2010).

Measures of Cognition. The PASAT, a paced addition test of working memory and processing speed, was selected as the cognitive task. Two variants of the PASAT were administered under single and dual task conditions. In one variant, the PASAT-3, digits were presented every three seconds. In the other, digits were presented every four seconds (PASAT-4).

The administration and scoring manual for the MSFC recommends the PASAT-3 be used to calculate the composite score. It further recommends administrating the PASAT with digits presented every two seconds if a greater cognitive challenge is desired. The MSFC guidebook provides scoresheets with predetermined digits, two for the 3-second PASAT and two for the 2-second PASAT. Thus, commercially available recordings for these presentations are available. These recordings include a 10-digit practice trial at each speed and two and 60-digit trials at each rate.

Because we used the PASAT as one component of a dual task experimental in which attention was required to complete both the PASAT and motor task, the 2-second PASAT was deemed too challenging. Furthermore, we sought to prevent muscular fatigue from confounding measures of force fluctuation and desired to shorten the duration of the PASAT task used in the dual task conditions. Because commercially available recordings for our PASAT variants were not available, we created our own recordings Digits were recorded and presented by the same female, human voice for all tasks. The digits presented in our tasks were obtained from the MSFC scoresheets. Table 3.1 summarizes the variants of the PASAT task created for this experiment.

Table 3.1. PASAT Variants.

Condition	Items	Interval (s)	Task Length (s)	MSFC Scoresheet Digit Presentation	Experimental Task(s)
PASAT-3 Practice	10	3	30	Form A - Practice Items	Single and dual
PASAT-3 Full	60	3	180	Form A	Single
PASAT-3 Shortened	30	3	90	Form B	Dual
PASAT-4 Practice	10	4	40	Form B – Practice Items	Single and dual
PASAT-4 Full	60	4	240	Form A	Single
PASAT-4 Shortened	30	4	120	Form B	Dual

Note: PASAT-3 = Paced Auditory Serial Addition Test, 3 second interval; PASAT-4 = Paced Auditory Serial Addition Test, 4 second interval. Form A and B obtained from Multiple Sclerosis Functional Composite guidebook.

Electromyography. Whole muscle surface electromyographic (EMG) activity of the tibialis anterior and medial gastrocnemius was obtained using a two-channel Delsys Bagnoli handheld EMG unit (Delsys, Natik,MA) as described in Chapter 2. Signals were amplified X1000, recorded through the Power 1404 (Cambridge Electronic Designs, Cambridge, UK) and sampled a 1 kHz using Spike 2.7 (Cambridge Electronic Designs, Cambridge, UK). Threshold for noise was set at 0.005 volts (V).

Experimental Protocol

The primary aim of this experiment was to determine if the dual task effects of cognitive-motor tasks differ between people with MS and healthy controls. Thus, experimental tasks included single task measures of cognition, a single task measure of motor function, and simultaneous performance of the tasks.

Experimental sessions began by obtaining anthropometric data, administering questionnaires, and carrying out clinical measures of function, balance, and mobility. The three single-task cognitive trials, PASAT-3, PASAT-4, and SDMT, were then presented followed by motor steadiness tasks under single and dual task conditions. The order of single-task cognitive activities was presented in a randomized, counterbalanced manner within each sample as was the presentation order of the motor tasks. For dual-task trials, the primary cognitive tasks were variants of the PASAT and the primary motor task was maintaining a steady, non-fatiguing, submaximal isometric contraction at 15% MVIC.

Primary Cognitive Task. In the single task cognitive condition, participants completed both the full (60 item) PASAT-3 and full PASAT-4. An unscored PASAT-3 or PASAT-4 practice run was performed immediately before each scored trial. Participants completed at least one, but not more than three, practice trials. The order in which single-task measures of cognition were presented was counterbalanced within each sample. These cognitive measures included the full PASAT-3, full PASAT-4, and SDMT. PASAT responses were scored by counting the total number of correct responses and the number of correct dyads (two consecutive correct responses).

In the dual task condition, participants completed the 30-item (shortened) versions of the PASAT-3 and PASAT-4 while maintaining steady isometric contractions using visual feedback. Procedures for the force steadiness task are described in the successive section. Participants were provided at least one, but no more than three, practice runs using the same 10-item PASAT practice recordings used in the single task condition. Each PASAT recording began by identifying the task variant and a 5-second warning prior to delivery of the first digit. Participants were instructed to obtain the force target

when the PASAT recording began to play, being as accurate and steady as possible. Participants were told that the goal of the task was to "be as accurate and steady as possible and provide as many correct answers as possible." Participants were told to focus equal attention on both tasks. Each dual task PASAT run was followed by an MVIC to monitor for muscular fatigue.

Primary Motor Task. The primary motor task was submaximal force steadiness at 15% MVIC of the ankle dorsiflexors. This force was selected because the first experiment revealed 15% MVIC to be the steadiest submaximal isometric force in those with MS. During the first experiment, three participants not only completed the experimental tasks described in that study, but also performed a 4 minute (240 second) hold. Following this hold, MVIC was obtained and compared to the pre-hold measure. None of these participants experienced an MVIC decrease of more than 5%. Therefore, it was concluded that 15% MVIC was the optimal target for this experiment because it was a steady, non-fatiguing force that could be successfully maintained for the duration of this dual-task experiment.

Participants were positioned in an adjustable chair and prepped for EMG recordings of the tibialis anterior and medial gastrocnemius. A 27" monitor displaying a 15-second interval of real time force feedback was placed 1.0 meter in front of participants. MVIC magnitude and associated EMG activity were obtained for the purposes of setting target forces and normalizing EMG signal, respectively. Detailed experimental setup and procedures for obtaining MVIC are described in Chapter 2.

Participants completed a series of steady contractions at 15% MVIC under single and dual task conditions. First, each performed two 15-second single task trials preceded

by at least one practice trial. Participants were instructed to be as accurate and steady as possible during these contractions. Feedback and encouragement were not provided by the investigator during the task because it could not also be provided during the dual-task condition when the participant was required to attend to auditory stimuli from the PASAT and visual force feedback.

After determining MIVC and performing two steady 15-second contractions, participants completed three additional tasks, a 120 second single-task hold, a 90-second dual task hold with 30-item PASAT-3, and a 120-second dual task hold with a 30-item PASAT-4. Tasks were presented in a randomized counterbalanced order within groups. An MVIC was performed after each task to monitor for fatigue. The protocol for motor tasks is shown in Figure 3.1.

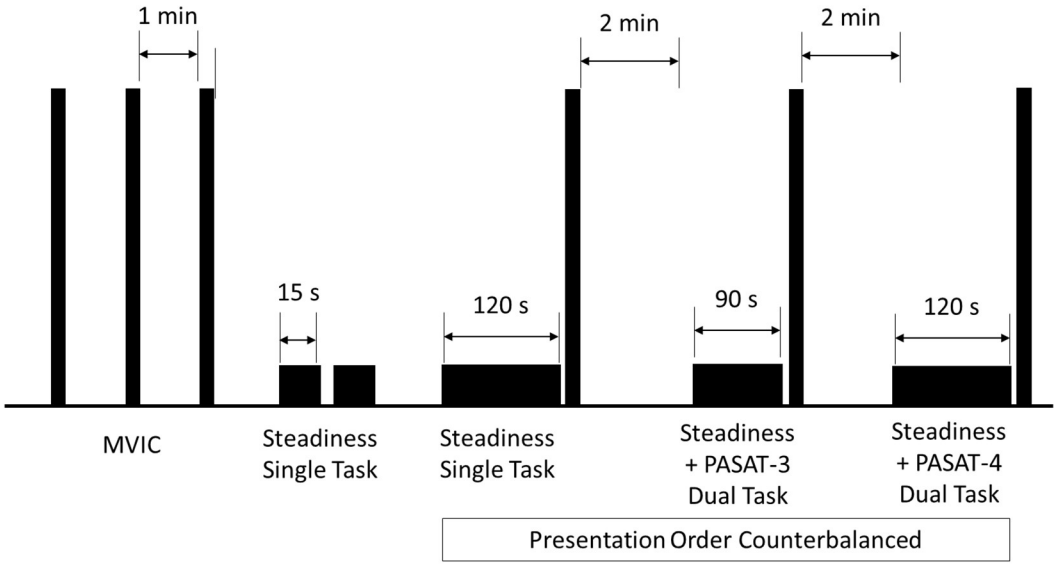


Figure 3.1 Experimental Protocol for Motor Tasks. At least three maximum voluntary isometric contractions were performed to calculate target force of 15% MVIC and normalize EMG. Participants performed one practice trial (not shown) prior to each measured trial.

Data Analysis

Measures of Force. Voltage output from the force transducer was converted to torque (Nm) as described in Chapter 2. Absolute (SD) and relative (CV) measures of force fluctuation were calculated for all submaximal holds. The 90 and 120-second tasks were analyzed in intervals and as a whole. For intervals, each hold was divided into 15-second intervals and the middle 5-second intervals analyzed for steadiness. This resulted in six segments for the PASAT-3 dual task condition and eight segments for the PASAT-4 and single-task hold. Whole task analysis included all data for the middle 85 seconds of the PASAT-3 dual task condition and the middle 115 seconds of both the PASAT-4 and single-task isometric hold. For all segments, steadiness was quantified as both the standard deviation (SD) of torque and the coefficient of variation (CV). SD was measured directly and CV was calculated by dividing the SD by the mean force (CV% = SD/mean force x 100%).

Electromyography. As described in Chapter 2, EMG was ascertained using RMS values during the same time periods used to analyze force. An attempt was made to calculate coactivation by dividing the agonist RMS value by that of the agonist and multiplying by 100%. This was not possible due to inadequate signal to noise ratio in the medial gastrocnemius.

Dual Task Effect. Dual task effects for both motor and cognitive performances were calculated for the isometric force steadiness tasks and the TUG. DTE was calculated by dividing the difference between dual and single task performance scores by the single task score. Negative scores indicate a negative dual task effect, or a dual task cost. Positive scores indicate a positive dual task effect, or dual task benefit.

For cognitive tasks, the number of correct responses was the outcome of interest. Because higher scores indicated better performance, the following equation was used to calculate DTE on cognition using the number of correct PASAT responses, number of PASAT dyads, and accuracy rate (accurate responses/s) for the TUGc.

$$DTE\ \% = \frac{(dual\ task - single\ task)}{single\ task} \times 100\%$$

Conversely, lower scores on motor variables indicated better performances. Thus, the following equation was used to calculate DTE on motor performance using the time required to complete the TUG (s) and CV (%) of torque of a steady, submaximal contraction.

$$DTE\ \% = \frac{-(dual\ task - single\ task)}{single\ task} \times 100$$

Statistical Analysis

Data were analyzed using IBM Statistical Package for Social Sciences, Version 26, an online calculator for effect size (Ellis, 2009), and an online calculator for Fisher's r to z transformation to determine significance of group differences in correlation coefficients (Lowry, 2019). Alpha was set to .05. Data are expressed as mean and standard deviation, $\overline{X}$ (SD), in the text and mean and standard error of the mean, $\overline{X}$ (SE), in figures. Variability of distributions was checked with Levene's Test for Equality of Variance for comparison of two samples and Mauchly's Test of Sphericity with three or more samples. When sphericity was violated with an epsilon value of .75 or greater, the

Huynh-Feldt correction was applied. When sphericity was violated with an epsilon value below .75, the Greenhouse-Geiser correction was applied.

Effect sizes were calculated for pairwise comparisons using calculated using Hedges' g when standard deviations were similar between groups and Glass' Δ when Levene's test revealed differences in variance between groups (Lakens, 2013). Effect sizes for pairwise comparisons made with the Mann Whitney U test are reported as r^2. These nonparametric effect sizes were calculated in Excel, first by determining the value of r ($r = \frac{z}{\sqrt{n}}$), then squaring the value (r^2). Partial eta squared (η_{p2}) was used to report significance for ANOVA.

Participant characteristics were compared between groups using independent t-tests and Mann-Whitney U for ordinal data. Analyses of variance (ANOVA) with repeated measures on within subjects factors were used to analyze force fluctuation (CV), cognitive performance (correct PASAT responses and dyads), and dual task effects for motor and cognition. The between-group factor in all analyses was disease status (MS, control). When the F-statistics attained significance, post hoc comparisons were made using independent and dependent t-tests to examine differences in DTE.

Associations between DTE and other variables were explored using Pearson's product moment correlation coefficients (r) for normally distributed ratio and interval level data and Spearman's rank correlation coefficient when an ordinal measure was explored.

RESULTS

Participant Characteristics. MS and controls were similar in age, BMI, wellbeing (PROMIS), and maximal ankle dorsiflexion torque. All participants completed high school and at least one year of college. The MS group had higher mean scores of depression and fatigue and performed poorer on physical activity and cognitive measures. See Table 3.2.

MS-specific characteristics are reported in Table 3.3. Our sample had a mean MSFC score of 0.31, indicating that they functioned slightly better than the population of people with MS. The PDDS mean of 1.92 indicates that those in our sample perceived that they had mild to moderate MS-related disability that did not limit walking ability.

Clinical Measure of Dual Task Effect. Motor and cognitive DTEs were calculated using two common clinical measures, the TUG motor task and Serial 3 backward counting task. The DTE of cognition on motor performance was calculated using the amount of time (s) required to complete the TUG under single and dual task conditions. Because the lengths of time for each TUG trial differed, it was not possible to provide a single task cognitive trial of an identical duration. Therefore, DTE on cognitive performance was reported as the rate of accurate responses per second, allowing a relative comparison between the single and dual task conditions.

Both the control and MS groups provided a similar number of responses during the TUGc task (Serial 3) [$t(24) = .77$, $p = .448$]. People with MS were slower in performing the TUG and TUGc and also experienced a greater negative motor dual task

effect. Controls performed better for the single task condition of counting backward by 1, 3, and 7 and also had a greater accuracy rate during the dual task TUGc. See Table 3.4.

Table 3.2. Participant Characteristics

Variable	MS (n=13; 2 males)	Control (n=13; 1 male)	*p*	Effect size
Age, yr	48.23 (10.19)	46.46 (5.53)	.587	
Height, cm	165.98 (7.55)	169.49 (8.81)	.286	
Mass, kg	76.96 (12.75)	84.07 (16.557)	.232	
BMI, kg/m^2	28.11 (5.50)	29.11 (4.19)	.608	
College completed, yr	6.08 (3.35)	9.27 (3.21)	.020*	0.94
PROMIS	37.46 (6.63)	42.08 (5.95)	.064	
CESD	8.92 (5.35)	4.23 (4.30)	.018*	0.22†
MFIS Total	35.54 (12.55)	9.92 (11.35)	<.001*	0.56†
MFIS Physical	16.38 (7.70)	3.38 (5.50)	<.001*	0.52†
MFIS Cognitive	16.69 (7.63)	6.08 (5.68)	.002*	0.38†
MFIS Psychosocial	2.46 (1.90)	0.46 (0.78)	.003*	0.33†
25FWT, s	5.54 (1.69)	3.75 (0.39)	.003*	1.41
9HPT, s	21.71 (4.20)	17.56 (1.32)	.002*	1.29
PASAT-3, n	48.08 (8.91)	56.08 (2.90)	.008*	1.17
PASAT-3, dyad	39.00 (12.67)	51.23 (5.85)	.006*	1.31
SDMT	48.77 (8.40)	64.15 (10.57)	<.001*	1.56
BBS	52.23 (5.64)	56.00 (0.00)	<.001*	0.73†
FGA	21.08 (5.204)	29.46 (0.66)	<.001*	0.72†
Ankle dorsiflexion MVIC, Nm	13.54 (6.07)	15.08 (5.45)	.503	

Note: Values expressed as mean (SD); * $p < .05$; Effect size reported in Hedges' g or r^2(†).BMI = Body mass index, PROMIS = Patient Reported Outcomes Measurement Information System Global Items, CESD = Center for Epidemiologic Studies Depression Scale, MFIS = Modified Fatigue Impact Scale, 25FWT = 25-foot Walk Test, 9HPT = 9-hole Peg Test, PASAT-3 = Paced Auditory Serial Addition Test, 3 second interval, SDMT = Symbol Digit Modalities Test, BBS = Berg Balance Scale, FGA = Functional Gait Index, MVIC = Maximum voluntary isometric contraction

Table 3.3: MS-Specific Participant Characteristics.

Variable	MS (n=15; 5 male)
MS Duration, months	161.22 (106.28)
MSFC	0.31 (0.35)
PDDS	1.92 (1.66)
FAMS Total	172.15 (28.17)
FAMS Mobility	19.38 (4.70)
FAMS Symptoms	23.62 (4.81)
FAMS Emotional Well-Being	25.38 (3.80)
FAMS General Contentment	22.00 (5.07)
FAMS Thinking and Fatigue	19.54 (6.53)
FAMS Family/Social Well-Being	23.46 (5.13)
FAMS Additional Concerns	38.77 (7.36)

MSFC = Multiple Sclerosis Functional Composite, PDDS = Patient Determined Disease Steps, FAMS = Functional Assessment of Multiple Sclerosis

Motor Dual Task Effect. Force fluctuation, expressed as CV (%), was examined using repeated measures ANOVA with MS as a between subjects factor and a within subjects factor of task (85 second single task contraction, 115 second single task contraction, PASAT-3 dual task contraction, and PASAT-4 dual task contraction). Significance with associated large effects was observed for the within subject factor of task [$F(3,72) = 5.43$, $p = .002$, $\eta_{p2} = .18$] and between subjects effect of MS status [$F(1,24) = 11.37$, $p = .003$, $\eta_{p2} = .32$]. There was no interaction of MS and task ($p = .998$).

Table 3.4: Clinical Measure of Dual Task Effect. Comparisons of single and dual task performance between MS and control for TUG and TUGc.

Variable	Task	MS	Control	*p*	Effect size
TUG, s	Single	8.02 (2.65)	5.42 (0.59)	.004*	1.31
TUGc, s	Dual	9.69 (3.03)	6.09 (0.84)	.001*	1.57
DTE motor, %		-21.79 (13.84)	-12.31 (8.02)	.043*	0.81
Serial 3, n/s	Single	0.29 (0.16)	0.51 (0.15)	.001*	1.37
TUGc, n/s	Dual	0.37 (0.11)	0.64 (0.13)	<.001*	2.17
DTE cognitive, %	Dual	0.73 (1.14)	0.30 (0.27)	.212	
Backward Counting by 1, n/s	Single	0.76 (0.19)	0.91 (0.15)	.037*	0.88
Serial 7, n/s	Single	0.16 (0.10)	0.26 (0.13)	.027*	0.84

Note: Values expressed as mean (SD). Effect size reported as Hedge's g.
TUG = Timed Up and Go; TUGc = Timed Up and Go Cognitive; DTE = Dual Task Effect; n/s = number of correct responses per second

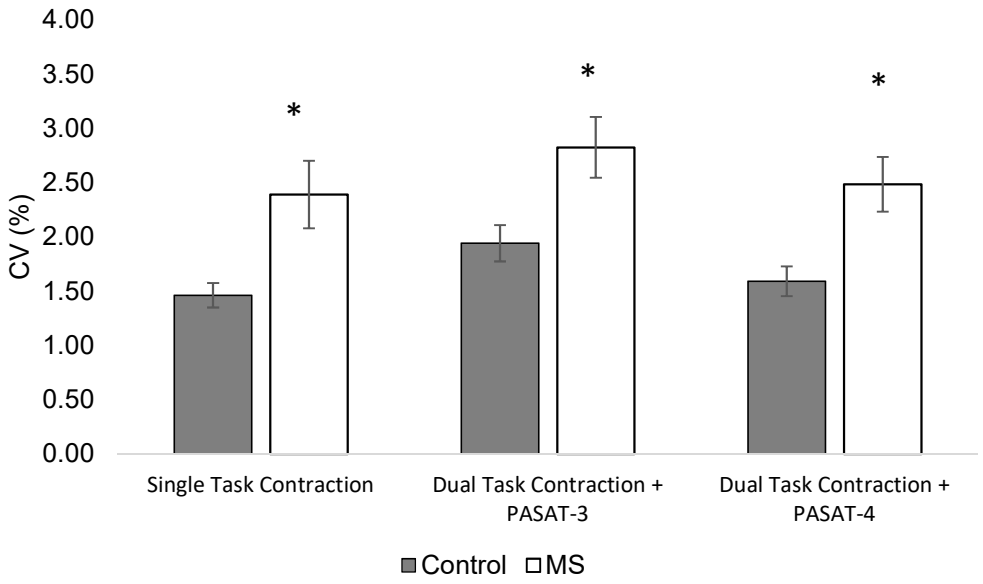


Figure 3.2 Coefficient of Variation in Single and Dual Task Conditions. CV for submaximal isometric steadiness task shown in the single task condition and two dual task conditions. In all conditions, those with MS were less steady than controls.

For controls, there was a difference in CV between the single task and PASAT-3 dual task [$t(12) = -4.66$, $p = .001$, $g = 1.70$], but not the single task and PASAT-4 dual task [$t(12) = -1.42$, $p = .182$]. For those with MS, there was no difference in CV between the single task condition and the PASAT-3 dual task condition [$t(12) = -1.56$, $p = .145$] or PASAT-4 dual task condition [$t(12) = -0.28$, $p = .786$]. Thus, controls were steadier than those with MS for all tasks and experienced a significant increase in fluctuation for the more challenging cognitive task, but not for the less challenging task. Within the MS group, force fluctuation did not change in any condition. The magnitude of the force CV was the same for the single task, PASAT-3 dual task, and PASAT-4 dual task conditions. Force fluctuation values for both groups across the three conditions is shown in Figure 3.2. Only the 120-second contraction, corresponding to the length of the PASAT-4, is illustrated as there were no within group differences for CV for the 90-second single task

contraction and 120-second single task contraction [Control $t(12) = -.57$, $p = .580$ and MS $t(12) = .42$, $p = .679$].

The DTE on motor performance was calculated using the CV of torque produced across the three tasks. DTE was calculated for the PASAT-3 using CV from the middle 85-second interval of the task. DTE was calculated for the PASAT-4 using CV from the middle 115-second interval of the task. To determine if performance varied over the duration of the task, each trial was divided into 15-second segments and DTE calculated for the middle 5-second interval of each segment. There were no within subjects effects for interval on the six segments of the PASAT-3 for controls or those with MS [$F(5,120) = 2.15$, $p = .064$]. The same within subjects finding was observed for the eight segments of the PASAT-4 for both controls and those with MS [$F(3.64, 87.18) = 0.70$, $p = .584$]. Because there were no within group differences among these segments, the data were analyzed using the entire 85-second segment during which the PASAT-3 was performed and the 115-second segment during with the PASAT-4 was performed. For each condition, data were analyzed five seconds after the presentation of the first PASAT digit.

All participants experienced a motor task cost, or negative dual task effect on force fluctuation, with the addition of the cognitive task. However, the magnitude of this effect was not equivalent in all circumstances. Within group comparisons of DTE between the PASAT-3 and PASAT-4 dual task conditions revealed that the negative DTE was significantly greater for the PASAT-3 and PASAT-4 [$t(12) = -4.61$, $p = .001$, $g = 1.71$]. In contrast, this within group difference for the MS group was not statistically significant [$t(12) = -1.75$, $p = .106$]. Furthermore, between group differences of DTE for

the PASAT-3 and PASAT-4 dual tasks were not significantly different as reported in Table 3.5.

Table 3.5. Dual Task Effect on Motor Performance

Dual Task Condition	DTE %		*p*
	MS	Control	
PASAT-3	-42.66 (43.85)	-29.47 (20.42)	.340
PASAT-4	-24.58 (39.17)	-6.67 (20.37)	.156

Note: Values expressed as mean (SD)
DTE= Dual task effect

Cognitive Dual Task Effect. The effect of the force steadiness task on cognition was calculated for the PASAT-3 and PASAT-4 using both the number of accurate responses and the number of correct dyads. Each task involved presentation of 30 digits. The highest possible score when using the total number of correct responses was 30. The highest when using dyads was 29. Controls performed better than those with MS for all tasks and the effect sizes were large (Table 3.6). Moderately strong to strong correlations existed between the 30-item PASAT-3 used in the dual task condition and the 60-item PASAT-3, included in the MSFC composite score, but these correlations were different within each group [MS r (11) = .96, p = < .001; Control r (df) = .64, p = .019. The significance of the difference between the two correlations was high [Fisher's r to z = 2.40, p = .016].

Post hoc testing revealed that the DTE on cognition was not different between groups for the PASAT-3 regardless of scoring method [number correct t (24) = 0.39, p =

.970; dyads correct t (24) = .467, p = .645]. However, the converse was observed for the PASAT-4 conditions. When using the number of correct PASAT-4 responses to calculate the effect on cognition, controls experienced a lower DTE [-4.39 (5.38)] than those with MS [-11.47 (7.75); t (24) = 2.71, p = .012, g = 1.18]. The same was observed when using dyads to determine the DTE on cognition during the PASAT-4 [Controls: -9.64 (12.11); MS: -25.21 (15.51); t (24) = 2.85, p = .009, g = 1.08]. Thus, those with MS did not perform as well as controls on PASAT tasks under dual task conditions, but the relative decrement in performance, determined by comparing the single and dual task PASAT scores, was not different between groups for the PASAT-3. The DTE on cognitive performance was lower for controls for the PASAT-4. The scoring method (number correct or number of dyads) did not affect the findings.

Table 3.6. PASAT Scores for Single and Dual Task Conditions

Task	Accurate Responses (n)				Accurate Dyads (n)			
	MS	Control	*p*	Effect Size	MS	Control	*p*	Effect Size
Single PASAT-3	24.92 (4.63)	29.0 (1.35)	.009*	3.02†	20.62 (7.33)	27.23 (2.59)	.008*	2.55†
Single PASAT-4	26.69 (3.55)	29.38 (0.77)	.019*	3.49†	23.15 (6.19)	27.77 (1.59)	.021*	2.91†
Dual PASAT-3	21.62 (3.86)	26.31 (2.69)	.001*	1.37	14.85 (6.45)	22.31 (5.28)	.004*	1.44
Dual PASAT-4	23.69 (4.09)	28.08 (1.38)	.002*	3.18†	17.54 (6.32)	25.00 (2.92)	.001*	1.47

Note: Values expressed as mean (SD), * p < .05, Effect size in Hedges' g or †Glass's Δ

The DTE of the motor task on cognition was determined in two ways. First, it was calculated using the number of correct PASAT responses. A second calculation was

made using the number of accurate dyads. These four dual task cognitive conditions (PASAT-3 number, PASAT-3 dyad, PASAT-4 number, PASAT-4 dyad) were examined using a repeated measures ANOVA. A main effect of condition on dual task cognitive effect was observed [$F(1.29, 30.91) = 4.67$, $p = .003$].

Summary of Dual Task Effects. Figure 3.3 shows the dual task effects for both groups for all study measures. For force steadiness tasks, both groups experienced mutual inhibition, also called cognitive-motor interference. Both groups had impaired performances of both the motor (force steadiness) task and the cognitive (PASAT) task when performing two tasks simultaneously. However, both groups experienced a mild cognitive-priority tradeoff when performing the dual task version of the TUG. Whereas the motor performance was impaired and all participant walked slower, the cognitive performance improved slightly.

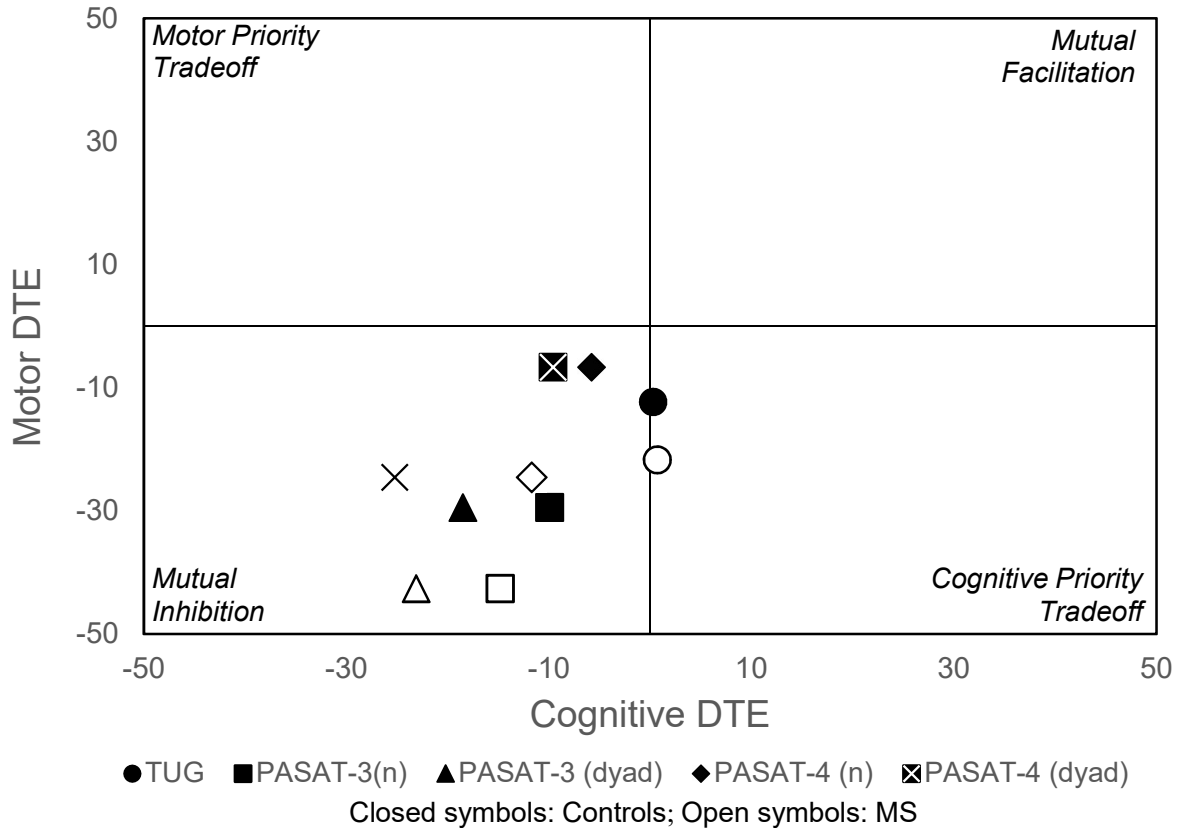


Figure 3.3 Summary of Dual Task Effects. For the TUG dual-task (circles), participants experienced a slight cognitive-priority tradeoff as cognition improved at the expense of walking speed. Dual tasks involving force steadiness and PASAT resulted in mutual inhibition as performances of both tasks declined. Although controls performed better on all tasks, the only significant difference in dual task effects was the dual task effect on cognition for the PASAT-3. PASAT scoring method (dyad or n correct) did not alter the significance of the findings.

Muscle Activation. As described in Chapter 2, an attempt was made to calculate muscle coactivation for the ankle by dividing the normalized magnitude of the tibialis anterior EMG by the normalize value of the medial gastrocnemius during the same periods analyzed for dual task effect. Coactivation could not be calculated because surface EMG measures for the medial gastrocnemius did not exceed the threshold for noise in both controls and those with MS.

Salient Associations. Associations between cognitive measures and years of college were explored because the number of years of college was different between the control and MS groups. In both groups, there were no significant associations between years of college and DTEs [Controls: PASAT-3 (r = .00PASAT-4; MS PASAT-3 PASAT-4], backward counting accuracy rate (1, 3, and 7), or PASAT-3 (single responses or dyads). In the control group only, there were moderate relations between years of college and the PASAT-4 [number accurate, r = .56, p = .045 and dyads, r = .61, p = .027. There were no significant associations between PASAT-4 scores in any condition in those with MS.

DISCUSSION

The design of this study is novel in MS research. It is the first to report reciprocal cognitive and motor dual task effects of for low-force isometric contractions necessary for performance of typical activities of daily living. It is also unique in that other published dual cognitive-motor task studies typically present a cognitive task at a single level of difficulty while we manipulated the interval at which stimuli were delivered in our task. Finally, we specifically instructed participants to devote equal attention to both tasks, whereas most dual task studies in MS have not reported specific prioritization instructions given to participants.

The purpose of the study was to examine dual task effects of cognitive-motor task performance in people with MS. We hypothesized that both controls and those with MS would experience motor and cognitive dual task costs and that these costs would be

greater in the MS group. We also hypothesized that additional time allotted for cognitive processing would lessen the negative effect exerted on cognition by addition of the motor task.

Consistent with our hypothesis, all participants experienced a dual task cost that negatively affected motor performance (Table 3.5). Contrary to our hypotheses, the magnitude of this dual task effect was not greater in people with MS and the negative effect of the more challenging cognitive task (PASAT-3) did not affect groups equally. Within the control group, there was a greater DTE on motor with the more challenging cognitive task. Within the MS group, the negative motor DTE was not different between the more and less challenging cognitive tasks. Between group comparisons of motor dual task effects revealed no significant differences between controls and people with MS at either level of cognitive challenge, possibly due to a ceiling effect. Although motor DTE, the relative change in performance between single and dual task conditions, was not different between groups, the MS cohort experienced greater force fluctuation in all three conditions (single task, PASAT-3, PASAT-4). This shows that people with MS experience a greater absolute decrement in motor performance when dual-tasking, but that the relative decline between single and dual task conditions is not different from what is experienced by controls regardless of the task difficulty selected in this experiment. Despite this, people with MS are still less steady than controls at all levels of force.

We observed a similar pattern of effects when examining the dual task impact of the motor task on cognitive performance. As with force fluctuation, those with MS did not perform as well as controls on PASAT tasks for both single and dual task conditions.

Additionally, in MS, the DTE on cognitive performance with addition of the motor task was no different between groups when stimuli were presented at a faster pace (PASAT-3). However, controls were better able to take advantage of extra processing time afforded during the PASAT-4 and experienced lower a lower DTE on cognition than the MS group.

The clinical measure of dual task effect, TUGc, also revealed different effects of dual tasking on cognitive and motor performances. Under single task conditions, controls performed better than the MS group. Controls completed the mobility component in less time and had a better rate of accurate responses per second. Interesting, both groups experienced a cognitive improvement (dual task benefit) and motor decrement (dual task cost) with dual tasking. Unlike the laboratory measure of force fluctuation that had a fixed length, subjects were able to alter the length of the TUG by walking slower, allowing more time to provide cognitive responses. Thus, both those with and without MS traded off motor performance for a cognitive benefit in the TUG even though the instructions emphasized that the goal of the task was to walk as quickly as safely possible and provide as many correct responses as possible. This is consistent with dual task studies of gait and cognition in MS in which participants walk slower and spend more time in a relatively stable period of double limb support under dual task conditions (Allali et al., 2014; F. Hamilton et al., 2009; Kalron et al., 2010; Sandroff, Benedict, et al., 2015).

The advantage of reporting the rate at which accurate answers are delivered is that a direct comparison can be made between tasks of different lengths. However, in this study the greatly different lengths of the TUGc and 30-second Serial 3 task may have

confounded our result. Caution should be used when interpreting our TUGc findings. Our data suggest cognitive facilitation with the addition of the mobility task. However, a relevant limitation to our methods is the discrepancy between the duration of the cognitive task in the TUGc and in the dual task counting backward trial. It is possible that the TUG findings do not indicate improved cognitive performance while walking, but rather suggests a cognitive priority tradeoff, an unconsciously selected strategy that improves gait stability and increase opportunities to engage in the cognitive task.

Opportunities exist to further determine how dual cognitive motor tasks affect those with MS. Prior works using gait as a motor task have shown inconsistent findings, with some reporting greater negative motor effects of an added cognitive task in MS (F. Hamilton et al., 2009; Kalron et al., 2010; Mofateh et al., 2017; Pau et al., 2018; Sandroff, Benedict, et al., 2015) and others reporting no difference (Learmonth et al., 2015; Nogueira et al., 2013; Saleh et al., 2018). Our findings are consistent with a recent systematic review by Learmonth (Learmonth et al., 2017) that examined 13 controlled studies in MS that reported both cognitive and motor DTEs. All but two studies reported 95% confidence intervals spanning zero indicating that both healthy controls and those with MS experienced similar negative dual task effects. Learmonth concluded that differences in cognitive motor interference (CMI), the decrement of both cognitive and motor performances, was minimal between healthy controls and those with MS. We also observed negative dual task effects on cognition and motor performances, but these effects were similar between groups.

Although our control group completed more college, there was no association between this variable and the SDMT or any variant of the PASAT. This suggests that the

constructs of these variables differ. Whereas the PASAT is considered a measure of processing speed and working memory (Archibald & Fisk, 2000; Chiaravalloti et al., 2013), it is likely that years of higher education is more strongly influenced by aphysiological factors. Therefore, it is likely that this different did not confound our observations.

Participants also differed from controls on health-related measures. The MS group had greater scores of depression, but the effect size was small. They also had higher levels of fatigue. It is difficult to control for these differences because both depression (Flachenecker et al., 2002; Greeke et al., 2017) and fatigue (Fisk et al., 1994; L. Krupp, 2006) are common in MS. Furthermore, our sample with MS is representative of the typical population used to standardize the MSFC composite score. Our participants with MS fared slightly better than the population estimate on overall function indicated by the MSFC score (z-score) of 0.31.

In summary, people with MS performed poorer on both clinical and laboratory measures of cognition and motor function than matched controls. Dual task effects on motor performance were not different between groups. Dual task effects on cognition were not different between groups except for the PASAT-4 in which those with MS experienced a greater DTE. This suggests that participants with MS prioritized the motor task over the cognitive task with the laboratory-based measure and prioritized the cognitive task over the motor task in the clinical measure.

CHAPTER 4. DISCUSSION

This dissertation shows that isometric force steadiness is impaired in the upper and lower extremities of people with MS at very low forces under single task conditions, that people with MS experience decrements of cognitive and motor performance when dual tasking, and that these negative dual task effects are comparable to what is experienced by healthy controls.

There are limitations to the experiments performed. First, the MS samples in both experiments reported minimal MS-related disability using the PDDS and the mean MSFC scores indicated that our participants functioned only slightly better than the standard population used to calculate MSFC z-scores. Thus, the results may not translate to those who are more disabled. Second, we did not evaluate sensory function. Therefore, it is possible that undetected impairments in visual processing or somatosensory processing could confound the results, especially with regard to visual processing of force feedback required to perform the motor steadiness tasks. Finally, even though we had adequate statistical power to measure most variables, it is possible that our small sample sizes lacked sufficient power to detect smaller differences that may have been present in some measures.

This dissertation is the first to document isometric force fluctuation of upper and lower extremities in MS and found that there was no significant association between upper and lower extremity force steadiness across a range of forces in the same participants. This contrasts to findings of a study by Coghe and colleagues (2019) who also examined the association of MS-related impairment in the upper and lower extremities. Coghe reported kinematic profiles of people with MS performing motor tasks

with the upper and lower extremities and found that both limbs became more impaired as MS progresses and that these upper and lower limb impairments were moderately related. Coghe's findings suggest that diffuse MS-related changes in the CNS may produce motor impairments in various body segments. Our methods contrasted with Coghe in that we measured force fluctuation by performing relatively simple, identical tasks in the same muscle groups and Coghe recorded kinematic profiles of two different complex tasks, one discrete (moving the hand to the mouth) and one continuous (gait). It was also the first to examine effects of cognitive tasks presented with different levels of difficulty. This illustrates challenges of measuring associated impairment of the upper and lower limbs. Future research, especially in those minimally impaired by MS, should consider whether experimental tasks are discrete and heavily dependent upon feedforward control or continuous and more dependent upon feedback control, as well as the cortical representation for the body segments involved in performing the tasks. For example, fine motor tasks of the hand present challenges as the hand and wrist have a greater cortical representation in the motor and somatosensory cortices than lower extremity segments creating challenges for direct comparison. Additionally, gait tasks primarily involving lower limbs present challenges because control of gait is mediated by central pattern generators that lessen the attentional demand of walking.

Our variants of the PASAT task may have lacked sensitivity in detecting impairments and our participants, especially the healthy controls, may have experienced a ceiling effect of this task. We measured cognitive performance by counting accurate responses. However, future studies of dual task effects could be aided by use of a

cognitive task that allows measurement of not only accuracy, but also response speed, especially in people with MS who are known to have impairments in processing speed (Archibald & Fisk, 2000; DeLuca et al., 2004; Demaree et al., 1999; Moccia et al., 2016). This would provide a richer description of cognitive effects and determine if variability in timing of responses is associated with variability in motor task performances.

An n-back task of working memory in which cognitive demand is manipulated across conditions would be such a task and has previously been used in people with MS to document impairments in accuracy and response speed (Parmenter, Shucard, Benedict, & Shucard, 2006; Parmenter, Shucard, & Shucard, 2007). In a typical n-back task, participants view a monitor that briefly displays letters. Participants attend to each visual stimulus and reporting if it had been previously presented at a specified interval. Responses are collected via a key press in which one key is pressed if the stimulus was previously seen at the specified interval and another pressed if the stimulus was not. This application of the n-back would be useful in presenting different levels of cognitive difficulty, measuring accuracy, and measuring response timing. The modified PASAT used in this dissertation was able to present different levels of difficulty and measure accuracy. However, it was unable to measure response timing.

Interestingly, this dissertation initially sought to use the n-back task in lieu of the modified PASAT. Unfortunately, the visual processing demands of continually monitoring force feedback during dual task conditions while concurrently monitoring visual displays of n-back stimuli were deemed too demanding for our dual task paradigm. An attempt was made to substitute recorded stimuli (letters) for the n-back task. This was problematic because the spoken names of the letters of the English alphabet sound

similar. For example, the spoken names of letters such as B, C, D, and G are all predominated by the long-e vowel sound. Presenting vowels was undesired as participants could use them to aid memory by phonologically linking individual stimuli and presenting words was undesired because participants could create a narrative that aided performance. A final consideration was made to deliver n-back stimuli via monosyllabic nonsense words. Further exploration revealed that humans can more easily distinguish less frequent sounds (kw) from more common sounds (th). Because the aims of this dissertation did not include development and validation of a new measurement, it was decided that variants of the PASAT would be used. However, availability of a valid auditory n-back task would be a useful component of dual task experiments that require visual processing of another stimulus.

From a mechanistic perspective, both muscle function and cortical function could be examined in more detail while varying the conditions under which the tasks are performed. As force fluctuation is associated with variability in motor unit discharge rates, we could replicate this study replacing our single-channel surface EMG recordings for intramuscular single motor unit recordings or an array of surface EMG electrodes that allow recording over a large area of muscle (Drost, Stegeman, van Engelen, & Zwarts, 2006; Merletti, Holobar, & Farina, 2008). It would be especially interesting to apply these techniques while replicating our tasks at the very low force targets in which we observed increased CV in our MS group.

Furthermore, because muscle fatigability is a common symptom of MS, it would be beneficial to measure motor unit discharge rates during fatiguing contractions as recent findings suggest that dual task abilty is impaired during fatigue in people with MS

using a choice reaction time task during a fatiguing finger flexion task (Wolkorte, Heersema, & Zijdewind, 2014).

While motor unit discharge rates may explain the final common output of the motor steadiness task, it is influenced by visual processing of force feedback and cortical processing of the voluntary goal-directed changes in neural drive to the muscle that result in force production. It is well established that humans heavily weight visual processing and that visual perturbations result in alterations of postural control (Shumway-Cook & Woollacott, 2012; Woollacott & Shumway-Cook, 2002). Although the effect of the quantity of visual feedback (Prodoehl & Vaillancourt, 2010) has been explored in motor tasks, the complexity of the visual environment has not. If visual processing is responsible for influencing the intention to alter force production and ultimately affect neural drive, it could mean that the environment in which we conducted our experiments influenced steadiness. One way to explore this would be to present force feedback via goggles that block all other visual stimuli. To manipulate visual complexity, force feedback could be displayed in three ways, against a plain background, framed by a complex pattern such as a checkerboard, and framed by a complex background with motion such as a scrolling checkerboard.

To better understand cortical contributions to dual task performances, fMRI could be a useful tool. A study exploring cortical areas associated with force steadiness in healthy adults has been published (Yoon et al., 2014). However, it is not known if these areas are influenced by secondary cognitive tasks. In MS research, lesion mapping, as opposed to calculating total of lesion load, provides insights into MS-related dual task impairment (Ruggieri et al., 2018) . Thus, static and functional imaging techniques may

aid in understanding of cortical behavior during dual task performance and possibly reveal associations between areas involved in dual task steadiness and lesion location in MS.

Another consideration in dual task studies of MS is the mode and difficulty of each task. Consistent with other research paradigms, cognitive dual tasks in this dissertation primarily tapped the central executive and phonologic loop, leaving the visuospatial component of working memory unexplored. A study of dual tasking using two cognitive tasks employed a design in which visuospatial working memory was measured using a task in which participants needed to attend to and recall spatial orientation of lines while performing an additional cognitive task. Determining optimal modes and dosages of motor and cognitive tasks would be of great clinical relevance.

In summary, this dissertation provides novel insights into isometric force steadiness and dual task performance in people with MS. The findings provide exciting opportunities to expand clinically relevant research.

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