CHARACTERIZATION OF PHYSICAL AND COGNITIVE FUNCTION, PHYSICAL ACTIVITY, AND SEDENTARY BEHAVIOR IN OLDER ADULTS WITH MULTIPLE SCLEROSIS

BY

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DISSERTATION

Submitted in partial fulfillment of the requirements
for the degree of Doctor of Philosophy in Kinesiology
in the Graduate College of the
University of Illinois at Urbana-Champaign, 2017

Urbana, Illinois

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ABSTRACT

Background: Older adults with multiple sclerosis (MS) experience age-related declines in physical and cognitive function that may be compounded by the disease and its progression. However, the extent to which impairments in physical and cognitive function are manifestations of MS and disease progression, reflective of the general aging process, or perhaps two detrimental processes exacerbating the synergistic effects of the other is relatively unknown. Further, there is very little known about managing the progression and consequences of MS in older adults. Physical activity participation might provide a protective or potentially restorative effect on the mechanisms associated with aging and MS that influence physical and cognitive function.

Objectives: The present study examined physical and cognitive function in 40 older adults with MS (i.e., 60 years of age and older) compared to 40 age- and sex-matched healthy older adults in the general population and the extent to which objectively measured physical activity and sedentary behavior were associated with these functions.

Methods: Participants initially underwent the cognitive assessments, followed by the physical function assessments. The order of tests was standardized and participants were provided seated-rest between the administrations of the physical function assessments. Participants were then instructed to wear an accelerometer and document wear time in a log book for a seven-day period after the testing session.

Results: Independent samples *t*-tests indicated that older adults with MS performed worse on all measures of physical function and one measure of cognitive function (i.e., information processing speed) compared to healthy controls. ANCOVAs indicated that older adults with MS engaged in less moderate-to-vigorous physical activity (MVPA) (minutes/day) and more sedentary behavior (minutes/day) compared to healthy controls. Partial Pearson correlations demonstrated that levels and patterns of physical activity were significantly associated with a majority of physical function variables but not cognitive function variables in both older adults with MS and healthy controls but to a greater extent in older adults with MS. Partial Pearson correlations further demonstrated that levels and patterns of sedentary behavior were significantly associated with a majority of physical function variables but not cognitive function variables primarily in older adults with MS. Linear regression analyses further demonstrated that the low levels of MVPA (minutes/day) partially accounted for differences in physical and cognitive function variables between older adults with MS and healthy controls.

Conclusions: The present results indicate that compared to healthy controls, older adults with MS experience large declines in all areas of physical function, but only one area of cognitive function (i.e., information processing speed), and engage in lower levels of MVPA and higher levels of sedentary behavior. Further, both levels and patterns of physical activity, namely MVPA, and sedentary behavior should be a focus of clinical rehabilitation and behavioral interventions for the promotion of healthy aging in older adults with MS.

ACKNOWLEDGMENTS

I would first like to thank God for blessing me with the opportunity to have spent the last five years learning, teaching, and conducting research – all of which I immensely enjoy and feel very passionate about. I would like to thank my advisor, Dr. Rob Motl, for everything during my time in the Exercise Neuroscience Research Laboratory. Rob always pushed me to be the best student, researcher, and person I could be. Rob's guidance and inspiration have been invaluable over the past five years. I want to thank my committee of Drs. Lara Pilutti, Bo Fernhall, and Steve Petruzzello for your guidance through this dissertation process. I greatly appreciate your time and willingness in providing thoughtful feedback and enthusiasm for this study. I feel very fortunate to have mentors who I look up to and who have made me a better researcher. I want to thank the other faculty and staff in the department for your constant assistance and support. I want to further acknowledge the funding for this study, the Paul D. Doolen Graduate Scholarship for the Study of Aging.

I would like to thank everyone that helped to make my time in the ENRL so very enjoyable, including Dee, Brian, Lara, Swathi, Shauna, Ipek, Yvonne, Lizzie, Julia, Dom, Sarah, Brynn, Emerson, and all undergraduate research assistants. Not only did I have amazing lab mates and fellow researchers, but good friends too. Perhaps the biggest thanks goes to the research participants who I have had the privilege of working with over the past five years. Without you, none of this is possible!

Lastly, I want to thank my family and friends for all the love and support you have given me, especially Brandon (and Nile) for always making me laugh and encouraging me to follow my dreams. No matter where the next few years take me, I know I will always have you by my side!

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Chapter 1:

Introduction

Multiple Sclerosis (MS) is a chronic, often progressive, neurologic disease involving inflammation, axonal demyelination and transection, and neurodegeneration within the central nervous system (CNS) (Trapp & Nave, 2008) with an estimated prevalence of 1 per 1000 people in the United States (Mayr et al., 2003). The damage within the CNS manifests as the accumulation of impairments and symptoms, including physical and cognitive disability (Confavreux & Vukusic, 2006a). Of the 400,000 adults living with MS in the United States, an estimated 30% of adults are between 55–64 years of age and 15% of adults are 65 years of age and older (Minden et al., 1993). There is additional evidence of a shift in the peak prevalence of MS among older adults. For example, in Manitoba, Canada, the peak prevalence of MS occurred at 35–39 years of age, with no documented cases beyond an age of 64 years, in 1984 (Marrie et al., 2010). By 2004, the peak prevalence was at 55–59 years of age, with cases of MS documented beyond 80 years of age (Marrie et al., 2010). This coincides with increased survival of those with MS as 90% of adults with MS may live to be 70 years of age or older (Hurwitz, 2011). Therefore, there are greater numbers of older adults living with MS than ever before, and this trend will continue over the next decades.

Older adults with MS undergo age-related declines in physical and cognitive function that may be compounded by the disease and its progression (Awad & Stüve, 2010; Stern et al., 2010). There is evidence of a faster rate of disability progression among older adults with MS (Minden et al., 2004) and older age is a predictor of reaching disability milestones in MS (e.g., median age for unilateral assistance during walking is nearly 65 years) (Confavreux & Vukusic, 2006b). Older adults with MS report limitations in activities of daily living (Finlayson & Van Denend,

2003) and express concerns about future losses of function and mobility that normally occur with aging (Finlayson, 2004). Aging is a risk factor for cognitive dysfunction. In a previous cross-sectional study, older adults with MS (59–74 years of age) performed worse on a single neuropsychological measure of information processing speed compared to healthy age- and sex-matched controls (Bodling et al., 2009). A very recent study demonstrated that the progression of decline in motor, or physical function, is amplified by aging in persons with MS; however, the degree of cognitive impairment did not seem to vary across the lifespan (Roy et al., 2016).

There are limitations of previous research that provide rationale for continued examination of physical and cognitive function among older adults with MS. For example, the existing research on physical function in older adults with MS has mostly included self-report measures (Finalyson, 2002; Finlayson & Van Denend, 2003; Finlayson, 2004). Those may suffer from validity, reproducibility, and applicability for use in different cultures and nations, similar to research in normal aging populations (Guralnik et al., 1989). There is further limited research examining direct, head-to-head comparisons of physical and cognitive function in older adults with MS and in older adults without MS or other neurological diseases. Therefore, direct, objective, and comprehensive research is absolutely warranted to examine the extent to which impairments in physical and cognitive function are manifestations of MS and disease progression, reflective of the general aging process, or perhaps two detrimental processes exacerbating the synergistic effects of the other.

There is very little known about managing the progression and consequences of MS in older adults. This is based on the fact that older adults with MS are often excluded from research. For example, there are 13 FDA-approved disease-modifying agents that represent the first line of therapy for persons with MS; these have only been tested in younger and middle-aged adults but

not older adults (Multiple Sclerosis Coalition, 2015; Stern et al., 2010). Some data suggest that these agents may have no effect on disease progression in older adults with MS (Shirani et al., 2015). Therefore, a focus on behavioral approaches, such as physical activity, may represent a novel approach for healthy aging with MS (Motl et al., 2016). Previous evidence suggests that older adults with MS are not engaging in sufficient amounts of physical activity for accruing health benefits and are engaging in high amounts of sedentary behavior (Klaren et al., 2016). However, there is much evidence on the benefits of physical activity in young and middle-aged adults with MS (Motl, 2014; Motl & Sandroff, 2015), older adults in the general population (Taylor et al., 2004), and in those with chronic diseases that impact mobility (de Vries et al., 2012). For example, in persons with MS, there is evidence of associations between physical activity and brain volume, walking performance, cognition, and symptoms of fatigue and pain (Motl, 2014). Physical activity participation may therefore provide a protective or potentially restorative effect on the mechanisms associated with aging and MS that influence physical and cognitive function (Keysor, 2003).

The current study involved the examination of physical and cognitive function in older adults with MS (i.e., 60 years of age and older) compared to age- and sex-matched healthy older adults in the general population and the extent to which objectively measured physical activity and sedentary behavior were associated with these functions. Based on previous research, the first hypothesis is that persons with MS would demonstrate greater impairments in all measures of physical and cognitive function compared to healthy older adults. The second hypothesis is that physical activity would be lower and sedentary behavior would be higher in older adults with MS compared to healthy older adults. The third hypothesis is that physical activity would be positively associated and sedentary behavior would be negatively associated with physical and

cognitive function in older adults with MS and in healthy older adults. Such data would provide information on the magnitude of decline in physical and cognitive function in older adults with MS and identify whether physical activity or sedentary behavior might account for the differences in function. The results of this study would further provide a foundation for clinical rehabilitation and behavioral interventions, such as physical activity, for the promotion of healthy aging in older adults with MS.

Chapter 2:

Review of Literature

The current review of literature provides information for developing the rationale for the present study of the characterization of physical and cognitive function, physical activity, and sedentary behavior in older adults with MS. This chapter first describes the pathophysiological mechanisms that contribute to physical and cognitive disability in persons with MS as well as the epidemiology of MS (i.e., incidence and prevalence). This chapter then discusses and reviews research examining physical and cognitive function in older adults with MS. This chapter further examines research on the associations of physical and cognitive function, physical activity, and sedentary behavior in MS. This chapter then concludes with a summary of the rationale and design of the current study.

Pathophysiology of MS

MS can be described as an immune-mediated and neurodegenerative disease of the CNS. The first diagnostic criteria were known as Charcot's triad, after Jean Martin Charcot, a French clinician and investigator who first recognized the disease in 1868 (Frohman et al., 2011). These criteria consisted of scanning speech, intention tremor, and nystagmus. Over the years, the diagnostic criteria have expanded and become more precise (i.e., Poser and McDonald criteria) that have greatly refined the ability to confirm a diagnosis.

MS often initially presents as clinically isolated demyelinating syndrome (CIS) and is associated with clear dissemination of silent or subclinical lesions in the brain or spinal cord (Frohman et al., 2011). Of the CIS cases, approximately 30–70% result in a diagnosis of MS (Miller et al., 2012). Inflammation is the hallmark of MS and the inflammatory processes are

caused by an autoimmune response within the CNS in which the body's own immune system attacks the myelin sheaths surrounding axons (Trapp & Nave, 2008). The acute inflammatory process involves an increase in adhesion molecules on the endothelium of the brain and spinal cord that allow autoreactive leukocytes to enter the CNS via the blood-brain barrier. These leukocytes then proliferate and trigger a cascade of events, including the activation of T-cells, microglia, and cytokines, that contribute to the acute inflammatory demyelination by reinforcing the attack on myelin, oligodendrocytes, and axons. This damage leads to the interruption of action potentials and axonal conduction and loss of remyelination capabilities, leading to the clinical signs and symptoms of MS (Vollmer, 2007). While many changes in the CNS occur in the white matter, there are also changes in the gray matter. The inflammation of the white matter is a result of T-cell activation whereas the gray matter inflammation seems to result from myelin reactive B-cells and the production of myelin-specific antibodies (Frohman et al., 2011).

As a result of the acute inflammation and associated demyelination, plaques, or lesions, are often formed in the CNS (Frohman et al., 2011). Glial cells in the CNS, such as astrocytes, accumulate in the areas of demyelination and this proliferation leads to the formation of glial scars that further prevent remyelination and any recovery processes to occur. There is also a chronic increase in the expression of sodium channels within the axon membrane, followed by the reversal of the sodium-calcium exchanger (Frohman et al., 2011). Both processes contribute to axonal dysfunction and neuronal degeneration. The resulting axonal transections are correlated with CNS atrophy and lead to the irreversible disabilities common in MS (Vollmer, 2007).

There are relapsing and progressive types of MS. The initial course of disease in approximately 85–90% of persons with MS is of the relapsing-remitting subtype (RRMS), that is characterized by relapses, or neurological exacerbations, followed by periods of remissions

(Trapp & Nave, 2008). Approximately 65% of persons with RRMS will further progress to another phase, referred to as Secondary Progressive MS (SPMS), after a period of approximately 19 years after initial diagnosis (Trapp & Nave, 2008). SPMS is characterized by progressive neurological decline, without definite periods of remission. In contrast to patients who initially present with RRMS, some patients experience a progressive course of disability from diagnosis, without any evidence of relapses or periods of remission. This is identified as Primary Progressive MS (PPMS) and describes approximately 10–15% of persons with MS (Trapp & Nave, 2008).

As a person with MS ages, the pathophysiological changes associated with the normal aging process may affect the severity of impairment and disability (Stern et al., 2010). Aging itself is characterized by the presence of a chronic, systemic low-grade inflammation and is influenced by chronic antigenic stimulations, such as infections (i.e., Epstein-Barr Virus (EBV)) and a general increase in the production of pro-inflammatory cytokines (i.e., IL-6 and TNF-α) (Sanai et al., 2016). There are further alterations in distribution and functionality of T-cells, particularly T-regulatory cells, and dysregulated microglia that lead to the neuroinflammatory pathology of aging (Kleinewietfeld & Hafler, 2014). These alterations, as well as the decreased thymic epithelial tissue and thymopoeisis associated with aging, contribute to reduced responsiveness to new antigens and subsequent increased frequency of infections. Lastly, in both MS and aging, there is the existence of bidirectional communication between the peripheral immune system and the brain mainly through immune molecules and cells that cross the blood-brain barrier. Therefore, the already compromised and dysfunctional immune system in MS will further be affected by the pathologies that occur with normal aging, thus driving the transition from RRMS to PPMS or SPMS.

Evidence has demonstrated that the level of inflammation typically decreases in persons with MS with age. Indeed, a previous study in elderly persons with MS demonstrated the density of pro-inflammatory cells and associated axonal injury to decline to levels similar to those found in age-matched controls (Awad & Stüve, 2010). However, neurodegeneration is amplified by factors related to aging, such as progressive degeneration of cells and loss of regenerative capacity (Knapowski, 2002). In aging individuals, the reduced capacity to regenerate injured tissues or organs is one of the hallmarks of senescence (Rist & Franklin, 2008). The age-related decrease in the efficiency of repair is often related to impaired stem and progenitor cell functionality, either through intrinsic or environmental changes in the aged tissue. Like other regenerative processes, remyelination is affected by aging. In persons with MS, there is further evidence that the failure of remyelination does not occur at the level of cell recruitment, but the lack of oligodendrocyte precursor cells differentiating into myelinating oligodendrocytes (Rist & Franklin, 2008). The tissue loss due to MS results in a 0.7%−1.0% loss of brain volume per year in persons with MS, compared to 0.1%−0.3% loss per year from normal aging in healthy subjects (Sanai et al., 2016). In the general aging population, there is a focal loss in thalamic volume; this loss is even more pronounced in persons with MS (Hasan et al., 2011) and is associated with physical disability (Niepel et al., 2006) and cognitive dysfunction (Derache et al., 2006). In a previous study, thalamic volume loss in persons with MS was correlated with Expanded Disability Status Scale (EDSS) scores after adjusting for natural aging and whole brain lesion volume (Hasan et al., 2011). This therefore suggests that MS pathology has a neurodegenerative component independent from lesions, especially in older adults, which contributes to the declines in function.

Epidemiology of MS

MS is one of the most common neurological diseases worldwide, with an estimated prevalence of more than two million cases (Kingwell et al., 2013) and a range of incidence rates of approximately 1 per 100,000 persons/years to 12 per 100,000 persons/years (Mayr et al., 2003). The disease typically presents in the 3rd or 4th decade of life (Mayr et al., 2003), and worldwide incidence of MS peaks at approximately 30 years of age (Noonan et al., 2002). In terms of sex differences, MS is more common in women such that women are affected three times more often than men (Noonan et al., 2002). MS is not considered a fatal disease, although the progression of the disease does cause significant life changes. Average survival has been reported to be approximately 38 years following diagnosis (Hirst et al., 2008). With the increase of disease-modifying therapies, lifespan has substantially increased over the past few decades among persons with MS (Hurwitz, 2011). Indeed, approximately 90% of adults with MS may live to be 70 years of age or older (Hurwitz, 2011). There is additional evidence of a shift in the peak prevalence of MS among older adults. For example, in Manitoba, Canada, the peak prevalence of MS occurred at 35–39 years of age, with no documented cases beyond an age of 64 years, in 1984 (Marrie et al., 2010). By 2004, the peak prevalence was at 55–59 years of age, with cases of MS documented beyond 80 years of age (Marrie et al., 2010). Of the 400,000 adults living with MS in the United States, an estimated 30% of adults are between 55–64 years of age and 15% of adults are 65 years of age and older (Minden et al., 1993).

MS is most prevalent in Western Europe and North America, followed by regions in Central and Eastern Europe and Australia (Koch-Henriksen & Sørenson, 2010). The regions with the lowest prevalence are Africa, Asia, and the Middle East. Further, MS seems to be most prevalent in areas above 40° latitude (Frohman et al., 2011). MS is therefore more common in

individuals with Northern European ancestry compared to individuals of African, Asian, or Hispanic descent (Mayr et al., 2003). In the United States, MS is most prevalent in the northern states compared to the southern states, with an overall prevalence of 1 per 1000 persons (Mayr et al., 2003).

While the cause of MS is still currently unknown, the risk of developing MS seems to be related to genetics as well as the environment. A previous analysis by an international consortium identified 29 disease susceptibility genes with direct or indirect influences on the immune system (International Multiple Sclerosis Genetics Consortium, 2011). For example, the risk of MS increases from 1% to 2–4% if a first-degree relative is affected (Frohman et al., 2011). Epidemiological data has also identified specific environmental risk factors for MS. For example, EBV is often associated with an increased risk of MS, especially if infected during adulthood (Lauer, 2010). Another study demonstrated that EBV is the only infectious agent that explains many of the key features of MS epidemiology (Ascherio & Munger, 2007). This study further reported that approximately 99% of persons with MS have previously been infected with EBV; this is compared to 95% of the general adult population (Ascherio & Munger, 2007). However, when compared to individuals infected with EBV in early childhood, the incidence of MS is 10-fold less among EBV-negative individuals and 2 to 3-fold greater among individuals infected with EBV later in life, based on a history of mononucleosis (Ascherio & Munger, 2007). Therefore, there is a 20-fold increase in risk among individuals with a history of mononucleosis compared with those who are EBV-negative. Tobacco smoking has further been identified as a risk factor for MS, with the relative risk for MS development approximately 1.5 for smokers compared with non-smokers (Wingerchuk, 2012). Vitamin D deficiency may also play a role in the susceptibility for the disease (Pugliatti et al., 2008). Due to the increase in prevalence of MS

in areas above 40° latitude (i.e., farther from the Equator) (Frohman et al., 2011), Vitamin D could be a potential mediator between latitude, or sunlight exposure, and risk for MS (Ascherio et al., 2010).

Physical and Cognitive Function in Older Adults with MS

Older adults with MS as well as healthy older adults in the general population experience impairments in overall function, with physical and cognitive function being two of the most affected domains (Stern et al., 2010). Indeed, the growing cohort of older adults with MS undergoes age-related declines in physical (e.g., ambulatory and balance dysfunction and muscle weakness) and cognitive function (i.e., information processed speed) that may be further compounded by the disease and its progression (Awad & Stüve, 2010; Stern et al., 2010). While there is much evidence on physical and cognitive function in older adults in the general population, there is limited evidence in older adults with MS, particularly using objective, performance measures of function. Further, the extent to which impairments in physical and cognitive function are manifestations of MS or of the aging process is generally unknown as there is scarce evidence of direct, head-to-head comparisons of function in older adults with MS and adults without MS or other neurological diseases. This section of the chapter will review the evidence on physical and cognitive function in older adults with MS and how they may differ from healthy older adults without MS.

Physical Function in Older Adults with MS

There is evidence of a faster rate of disability progression among older adults with MS (Minden et al., 2004) and older age is a predictor of reaching disability milestones in MS (e.g.,

median age for unilateral assistance during walking is nearly 65 years) (Confavreux & Vukusic, 2006b). In a study of persons with MS (n = 2156) examining demographic and clinical characteristics of those over and under 65 years of age, disability was significantly higher in older versus younger adults (Minden et al., 2004). Further, not surprisingly, a higher percentage of persons with MS over 65 years of age required a cane or bilateral support to walk 25 feet or were completely wheelchair dependent (Minden et al., 2004). In another study of 53 older adults with MS (mean age = 73 years), all participants reported problems with mobility (Klewer et al., 2001). As disability often increases with age, this same study reported average EDSS scores to be above 6.0 (requiring ambulatory assistance) in 96.2% of participants, and 69.8% required wheelchairs for their mobility (EDSS score above 6.5). Due to the high prevalence of assistive device use in older adults and high levels of disability, the risk of falling is also more common in older adults (Nilsagard et al., 2009).

There have been three qualitative studies that have examined disability and mobility loss from the perspectives of older adults with MS (Finalyson, 2002; Finalyson & Van Denend, 2003; Finalyson, 2004). The first study involved a descriptive analysis of three separate research studies conducted in Canada and the United States that examined the health profile of 440 older adults with MS (mean age = 64 years) (Finalyson, 2002). In the overall sample, the most common symptoms reported by participants were fatigue (82.6%), problems with balance (81.1%), and weakness (73.3%). Mobility impairment was further a major problem identified by participants. Overall, 13.4% of participants used a walking aid all the time and 14.1% were confined to a wheelchair. Difficulty with transportation was reported by 34.6% of participants. Participants also reported difficulties with activities of daily living, including inability to do

heavy housework independently (81.1%) or make a hot meal without assistance (50.2%). Further, 39.8% of participants rated their health as poor or bad.

In the second study, researchers examined the mobility experiences of older adults with MS, including mobility-related concerns and the consequences and challenges of mobility loss (Finlayson & Van Denend, 2003). A thematic analysis explained three factors contributing to mobility including the reality of having MS, mobility needs, and contextual factors. For example, participants expressed concerns about the continual declines in mobility and losing independence. The participants reported that MS affected their ability to get around and the importance of trying to remain in control over their mobility experiences. Further, participants' experiences of mobility were associated with mourning losses, taking action, and contemplating their future. The third qualitative study further examined the health-related concerns and needs of 27 older adults with MS (ages 55–81 years of age) (Finalyson, 2004). Overall, 'fear of the future' was identified as a predominant concern among the participants. Participants expressed concerns about experiencing further loss of mobility and independence and becoming a burden on caregivers.

One recent study examined the validity of the Short Physical Performance Battery (SPPB) in older adults with MS (Motl et al., 2015). The SPPB is an objective measure of physical function commonly used in older adults in the general population (Guralnik et al., 1994). This study reported that older adults with MS (50 years of age and older) (n = 48), had a median SPPB score of 9.0 (Motl et al., 2015), and this approached the expected SPPB score for non-disabled, healthy adults 71 years of age and older (mean = 9.2) (Guralnik et al., 2000). The lower extremity strength component of the SPPB demonstrated larger decrements in physical function (median score of 1.0 (IQR = 1.0)) compared to the other measurements of gait speed

(median score of 4.0 (IQR = 1.0)) and balance (median score of 4.0 (IQR = 1.0)), as lower scores are indicative of worse function.

Cognitive Function in Older Adults with MS

Cognitive impairment is present in an estimated 45–65% of persons with MS, with the core deficits as the slowing of information processing speed and episodic memory (Benedict & Zivadinov, 2011). Cognitive impairment is very detrimental in persons with MS and can have substantial influence on activities of daily living (Kalmar et al., 2008) and employment (Rao et al., 1991). One qualitative study examined the perceptions of cognitive function among aging adults with MS and their caregivers (Finlayson et al., 2009). The sample consisted of 279 dyads of persons with MS (mean age = 62.8 years) and their caregivers. Approximately 61% of persons with MS reported cognitive symptoms that interfered to some degree with their ability to engage in everyday activities. Further, approximately 62.7% of caregivers reported that their care recipients experienced cognitive symptoms. However, eighty dyads (28.7%) disagreed about the presence of cognitive symptoms in the person with MS.

A cross-sectional study of patients with MS (n = 84) from 45 to 81 years of age (mean age = 60.6 years) demonstrated that 48% of patients (n = 40) had cognitive impairment based on neuropsychological testing, including general cognitive functioning (Wechsler Adult Intelligence Scale (WAIS-III), psychomotor speed (Symbol Digit Modalities Test (SDMT), selective attention (Stroop Color Naming Test), working memory (Letter-Number Span Test (WAIS-III) and the Paced Auditory Serial Addition Test (PASAT)), verbal learning and memory (Hopkins Verbal Memory Test-Revised (HVMT-R)), non-verbal memory (Continuous Visual Memory Test), and executive function (Wisconsin Card Sorting Test short version (WCST-64) (Smestad

et al., 2010). The criteria for cognitive impairment was defined as a score of 1.5 standard deviations (SDs) below the mean normative values on at least one subtest in two of the four main functional areas (i.e., psychomotor speed, attention, learning/memory, and executive function). In general, the typical pattern of cognitive impairment was moderate in magnitude, within areas of information processing speed, attention, and memory. This study further demonstrated disease course type to be a predictor of cognitive impairment, such that persons with SPMS demonstrated increased cognitive impairment compared to persons with RRMS (OR = 2.74, 95% CI = 1.01–7.44, $p < 0.05$).

Another study demonstrated older adults with MS (59–74 years of age) (n = 245) performed worse on measures of information processing speed (i.e., Stroop Color and Word Naming Tests) compared to healthy age- and sex-matched controls (n = 188) (Bodling et al., 2009). That study further demonstrated reductions in information processing speed, across five age cohorts (i.e. 18–29, 30–39, 40–49, 50–58, and 59–74 years of age). However, there was no group by age interaction, such that persons with MS and healthy controls demonstrated similar trajectories of cognitive slowing across the five age cohorts. The major limitation of that study was the inclusion of a single domain of cognitive function (i.e., information processing speed) rather than a range of outcomes capable of capturing differences across multiple cognitive functions, particularly memory, given the high prevalence and impact of memory impairment associated with MS (Chiaravalloti & DeLuca, 2008) and aging (Peterson et al., 1997).

Regarding the mechanisms contributing to the cognitive decline with age in MS, evidence in young to middle-aged adults suggests the decline to be moderately related to the progression of lesion load in the whole brain and in specific regions, as well as overall brain atrophy (Amato et al., 2006). Lesion burden in frontal and parietal white matter was strongly

associated with performance on neuropsychological tests requiring sustained complex attention and working verbal memory (Sperling et al., 2001). Further, these associations were constant over a four-year period, suggesting that disruptions in the frontoparietal subcortical network may contribute to the increase in cognitive impairment with age in persons with MS.

Effects of Aging and MS on Physical and Cognitive Function

Determining the cause of worsening function in older adults with MS is very challenging as it is sometimes difficult to differentiate between the normal aging process and MS disease progression. Often, it may be the synergistic combination of the two that result in the overall decline in function (Sanai et al., 2016). As many of the pathological manifestations of aging and MS are similar (i.e., inflammation and neurodegeneration), so are various symptoms and impairments, such as reduced muscle strength, balance problems, and cognitive dysfunction. As persons with MS age, they are likely to have the same comorbidities as older adults in the general population, including hypertension, diabetes, cancer, or Alzheimer's disease, that may further contribute to physical and cognitive impairment (Ploughman et al., 2012). One recent study examined differences between persons with MS (n=698; 29−71 years of age) and healthy controls (n=226; 18−72 years of age) on motor (i.e., physical function) and cognitive performance across the lifespan (Roy et al., 2016). Linear regression models demonstrated an impact of aging in all motor and cognitive performance measures with a decline in performance with age. However, the age × MS diagnosis interaction effects were only significant for motor performance, but not cognitive function. Therefore, the aging process may affect physical and cognitive function differently in persons with MS. Additional research using direct comparisons

of older adults with MS and older adults without MS is warranted to truly examine and characterize the effects of aging and MS on physical and cognitive function.

Physical Activity, Sedentary Behavior, and Function in MS

There is very little known about managing the progression and consequences of MS in older adults, including the declines in physical and cognitive function. In the majority of previous research, older adults with MS are often excluded from trials. For example, the 13 FDA-approved disease-modifying agents that represent the first line of therapy for persons with MS have only been tested in younger and middle-aged adults but not older adults (Multiple Sclerosis Coalition, 2015; Stern et al., 2010). There is some data that suggest these agents may have no effect on disease progression in older adults with MS (Shirani et al., 2015). Therefore, a focus on physical activity may represent a novel approach for healthy aging with MS (Motl et al., 2016).

Previous evidence suggests that older adults with MS are not engaging in sufficient amounts of physical activity for accruing health benefits as well as engaging in high amounts of sedentary behavior (Klaren et al., 2016). For example, one previous study demonstrated that older adults with MS (i.e., ≥ 60 years of age) spend approximately 12 and 7 fewer minutes per day in moderate-to-vigorous physical activity (MVPA) compared with middle-aged (i.e., ages 40–59) and young adults (i.e., ages 20–39), respectively (Klaren et al., 2016). Only 14% of older adults with MS meet public health guidelines for MVPA (i.e., ≥ 30 min/day of MVPA), and this was significantly lower when compared with approximately 21% and 28% in middle-aged and young adults with MS. Further, this study demonstrated that older adults with MS spend significantly more time in sedentary behavior per day (554 minutes) compared with young adults

(510 minutes) (Klaren et al., 2016). The very low levels of physical activity and high levels of sedentary behavior in older adults with MS may further exacerbate problems associated with aging and disease progression.

By comparison, physical activity participation may provide a protective or potential restorative effect on physical and cognitive function in older adults with MS (Keysor, 2003). Indeed, there is much evidence on the benefits of physical activity in young and middle-aged adults with MS (Motl, 2014), older adults in the general population (Taylor et al., 2004), and in those with chronic diseases that impact mobility (de Vries et al., 2012). For example, in young and middle-aged adults with MS, there are numerous cross-sectional and longitudinal studies of the relationships between free-living or lifestyle physical activity and physical function, such as disability (Motl et al., 2012) and walking impairment (Motl et al., 2011). For example, one study demonstrated higher levels of premorbid physical activity lessened the rate of disability progression over a 24-month period in 269 persons with MS (mean age = 45.9 years), even when controlling for confounding variables such as sex or age (Motl et al., 2012). Another study examined the association between changes in lifestyle physical activity and walking impairment over a 6-month period in persons with RRMS (Motl et al., 2011). The results demonstrated direct effects between baseline physical activity and walking impairment (path coefficient = –0.31) and follow-up physical activity and walking impairment (path coefficient = –0.16). The second path coefficient established that a SD unit change of 1.0 in physical activity was associated with a SD unit residual change of 0.16 in walking impairment (Motl et al., 2011). Another cross-sectional study of 33 persons with MS demonstrated objectively measured physical activity to be significantly correlated with cognitive function, specifically processing speed (pr = 0.35), after controlling for sex, age, and education (Motl et al., 2011). A more recent study examined

physical activity and its association with volumes of whole brain gray matter and white matter and deep gray matter structures in a sample of 39 persons with MS (mean age = 48.7) (Klaren et al., 2015). Moderate-to-vigorous physical activity (MVPA), but not light physical activity (LPA), was significantly associated with whole brain gray matter volume (*pr* = 0.37), whole brain white matter volume (*pr* = 0.43), hippocampus *(pr* = 0.50), thalamus (*pr* = 0.38), caudate (*pr* = 0.54), putamen (*pr* = 0.37), and pallidum (*pr* = 0.50) volumes, even when controlling for sex, age, clinical course of MS, and EDSS score. These results suggest that that MVPA is associated with volumes of whole brain gray matter and white matter and deep gray matter structures that are involved in motor and cognitive functions in MS. The consequences of sedentary behavior have also been examined in previous research involving young and middle-aged adults with MS (Veldjuijzen van Zanten et al., 2016). One study demonstrated that greater sedentary time, measured using accelerometry, was significantly correlated with lower walking endurance (*r* = 0.40) and slower walking speed (*r* = 0.35) in a sample of 82 persons with MS (Hubbard & Motl, 2015). Another study demonstrated that higher levels of sedentary behavior were negatively associated with average daily step count and average number of minutes being active in a sample of 21 adults with MS (Cavanaugh et al., 2011). Other reviews have provided evidence that exercise training, a subtype of physical activity, demonstrated benefits across a spectrum of outcomes including inflammatory factors, neurotrophic factors, and CNS structures (Motl & Pilutti, 2012).

There have been few exercise training interventions designed for older adults with MS. For example, one randomized controlled trial (RCT) examined the effects of a 6-month exercise training DVD on a variety of physical function outcomes, including strength, mobility, flexibility, and balance, in a sample of 24 older adults with MS (50 years of age and older)

(McAuley et al., 2015). This study demonstrated a modest effect on the intervention on physical function. For example, participants demonstrated an increased SPPB score of ~0.30, a small, clinically meaningful difference. Another RCT examined the effects of a 12-week home-based exercise program targeting balance, walking, and lower limb muscle strength for reducing fall risk in a sample of 13 older adults with MS (50–75 years of age) (Sosnoff et al., 2014). Overall, this intervention reduced physiological fall risk in older adults with MS, and this reduced risk was associated with improvements in balance.

The Present Study

There are limitations of previous research that provide rationale for continued examination of physical and cognitive function among older adults with MS. For example, the existing research on physical function in older adults with MS has included self-report measures (Finalyson, 2002; Finlayson & Van Denend, 2003; Finlayson, 2004) that may suffer with validity, reproducibility, and applicability for use in different cultures and nations, similar to research in normal aging populations (Guralnik et al., 1989). There is further limited research examining direct, head-to-head comparisons of physical and cognitive function in older adults with MS and older adults without MS or other neurological disease. Research on physical and cognitive function in older adults with MS would greatly benefit from objective and comprehensive measures.

The current study involved the examination of physical and cognitive function in older adults with MS (i.e., 60 years of age and older) compared to age- and sex- matched healthy older adults in the general population and the extent to which objectively measured physical activity and sedentary behavior were associated with function. Figure 1 illustrates a model that guided

the current study including the mechanisms of aging and MS on physical and cognitive function and the potential effects of physical activity and sedentary behavior. Based on previous research, the first hypothesis was that persons with MS would demonstrate greater impairments in all measures of physical and cognitive function compared to healthy older adults. The second hypothesis was that physical activity would be lower and sedentary behavior would be higher in older adults with MS compared to healthy older adults. The third hypothesis was that physical activity would be positively associated and sedentary behavior would be negatively associated with physical and cognitive function in older adults with MS and in healthy older adults. Such data would provide information on the magnitude of decline in physical and cognitive function in older adults with MS and identify whether physical activity or sedentary behavior might account for the differences in function. Therefore, this study would provide information to further facilitate clinical rehabilitation and behavioral interventions, such as physical activity, for the promotion of healthy aging in older adults with MS.

Chapter 3:

Methods

Participants

The sample included 40 community-dwelling older adults with MS and 40 age- and sex-matched healthy controls aged 60 years and older. These participants were recruited from a mailing list of persons with MS in Illinois, a database of previous research volunteers, and a research advertisement posted on the website of the Greater Illinois chapter of the National Multiple Sclerosis Society (NMSS). The healthy controls were recruited through a campus-wide, email listserv. Participants were screened via telephone with the inclusion criteria for older adults with MS as: (a) 60 years of age and older; (b) diagnosis of MS; (c) relapse free in the last 30 days; (d) ambulatory with or without assistance (i.e., walk independently or walk with a cane/rollator); (e) willing and able to visit the laboratory for one testing session. The inclusion criteria for the healthy controls was the same except for the diagnosis of MS and relapse free in the last 30 days.

Measures of Physical Function

Timed 25-Foot Walk (T25FW). The T25FW was administered as a measure of walking speed as this measure has been identified as the best-characterized objective measure of ambulation in MS (Kiesseier & Pozzilli, 2012). Participants completed the T25FW twice, while walking as quickly as possible. The primary outcome was the average of the two walks (in seconds).

6-Minute Walk (6MW). The 6MW was administered as a measure of walking endurance as this measure is valid and reliable in persons with MS (Goldman et al., 2008). Participants

completed the 6MW as quickly as possible in a 75-foot hallway while performing 180° turns around cones placed at each end of the hallway. The primary outcome was total distance traveled (in feet).

Timed Up-and-Go (TUG). The TUG test was administered as an objective measure of functional mobility. This measure is routinely used in research with older adults (Podsiadlo & Richardson, 1991) and has been validated for use in persons with MS (Sebastiao et al., 2016). Participants completed the assessment by standing up from a chair (without the use of hands), walking 180° around a cone placed three meters in front of the chair, walking back to the chair, and then sitting down. If needed, participants were allowed to use assistive devices (i.e., cane or rollator) while performing the task. Participants were given two trials to complete the TUG test, and the average time across the two trials (in seconds) was computed as the final outcome.

6-Spot Step Test (6SST). The 6SST was administered as a measure of ambulatory function (Niewenhuis et al., 2006) as this measure has been validated in persons with MS (Sandroff et al., 2015). Participants completed the assessment by walking across a five-meter long and one-meter wide rectangular course, with five separate cones positioned on the ground, one and three meters from the starting line on the left side and two and four meters from the starting line on the right side, with the final cone positioned at the course's midline, five meters from the start line. Participants kicked the cones off of the marked position with one foot, alternating between medial and lateral sides of the foot. Each participant completed the 6SST four times: twice using their dominant foot, and twice using their non-dominant foot to kick the cones. The primary outcome was the average of the four trials (in seconds).

Short Physical Performance Battery (SPPB). The SPPB was administered as a measure of lower extremity function based on a three-part assessment, including standing balance, gait

speed, and chair rises (Guralnik et al., 1994; Guralnik et al., 1995). The SPPB has previously been validated in older adults (Guralnik et al., 1994) and older adults with MS (Motl et al., 2015). Standing balance was assessed by asking participants to maintain upright posture for up to 10 seconds per test while standing with feet in side-by-side, semi-tandem, and tandem positions. Those balance assessments occurred in a progressive order wherein participants needed to pass one test in order to attempt the subsequent, more challenging test. Gait speed was assessed based on the time taken by a participant to walk a four-meter course at a usual pace with the outcome of the fastest walk of two trials. Lower extremity strength was assessed by a chair stand test in which participants were instructed to sit in and fully rise from a chair five times as quickly as possible, without using arms for support. Participants were first asked to attempt and complete a single sit-and-rise before beginning the entire chair stand test. Performance scores for each SPPB individual assessment and a summary score aggregating the individual assessments was calculated as per standard SPPB protocol. Each of the three performance assessments was assigned a categorical score ranging from 0 (inability to complete a test) through 4 (highest level of performance) using standardized scoring, and the summary ranging between 0 and 12 was calculated by summing the standing balance, gait speed, and lower extremity strength categorical scores. Higher scores reflect better lower extremity function.

Measures of Cognitive Function.

The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). The BICAMS is a battery of three cognitive tests (Langdon et al., 2012) including measures of information processing speed (Symbol Digit Modalities Test (SDMT)) (Smith, 1982), verbal memory (California Verbal Learning Test-II (CVLT-II)) (Delis et al., 2000), and visual memory

(Brief Visuospatial Memory Test-Revised (BVMT-R)) (Benedict, 1997). The oral version of the SDMT involved pairing nine abstract geometric symbols with single digit numbers provided in a key. Participants were asked to voice correct numbers for unpaired symbols as quickly as possible for 90 seconds. Responses were recorded by the examiner, and the primary score was the total number of correct responses in 90 seconds. The CVLT-II involved the examiner reading a list of 16 randomly arranged words, with four words belonging to four categories (e.g., modes of transportation, furniture, animals, and vegetables) over five trials. After each trial, participants were instructed to recall as many words in any order. The overall score was expressed as the total number of correctly recalled words over the five trials. The BVMT-R involved three trials of the examiner presenting a 2 × 3 array of abstract of six geometric figures approximately 15 inches in front of the participant for 10 seconds. The examiner then removed the array and participants were asked to draw the array as precisely as possible, with the figures in the correct location. Each drawing was scored on a 0 to 2 scale, based on accurately drawing each figure and in the correct location. The primary outcome was the total score over the three trials, with a maximum score of 36.

Paced Auditory Serial Addition Test (PASAT). The 3-second version of the PASAT (Fischer et al., 1999) was administered as an additional measure of information processing speed in the auditory domain. In the PASAT, a series of random single digit numbers were presented to the participants at the rate of one number every three seconds via an audio recording. Participants were instructed to say the sum of the last two numbers that were presented on the recording. Prior to testing, the examiner provided an example of how to perform the task correctly, ensuring that the participant understood not to give running totals, but the separate sums of the two most recent numbers presented. Up to three practice trials, consisting of 11 random numbers, were

completed by the participant prior to testing. During the actual test, a series of 61 random numbers were presented at the same rate. The primary outcome was the number of correct responses given, with a maximum score of 60.

Sedentary Behavior & Physical Activity. Sedentary behavior and physical activity were objectively measured with ActiGraph GT3X+ accelerometers (Health One Technology, Fort Walton Beach, FL). The accelerometers were initialized using the low-frequency extension feature as this increases the sensitivity for capturing low frequency accelerations (i.e., slow walking). The raw activity data were downloaded using software (ActiLife 8) and the data was processed into two separate Microsoft Excel files. One file represented daily accelerometer wear time and the other file represented time spent in sedentary behavior (≤99 counts/minute), LPA (100–1,722 counts/minute), and MVPA (i.e., ≥1,723 counts/minute) for older adults with MS and time spent in sedentary behavior (≤99 counts/minute), LPA (100–2,016 counts/minute), and MVPA (i.e., ≥2,017 counts/minute) for healthy controls (Sandroff et al., 2012). These files further provided data on patterns of sedentary behavior and physical activity including number and average duration (minutes) of sedentary bouts (i.e., consecutive minutes with recorded counts of <100/minute sustained for more than 2 minutes); number and average duration (minutes) of long sedentary bouts (>30 minutes); and number and average duration (minutes) of activity bouts (i.e., >10 consecutive minutes with recorded counts of ≥100/minute) (Ezeugwu et al., 2015). Accelerometer wear time data were checked against participant recorded wear times from a log sheet and participants with ≥2 valid days (≥10 hours of wear time without periods of continuous zeros exceeding 60 minutes indicative of non-compliance) were included in the analysis (Motl et al., 2007).

Disability Status. All older adults with MS underwent a neurological exam by a Neurostatus-certified examiner to generate Expanded Disability Status Scale (EDSS) scores (Kurtzke, 1983) for describing the disability status of the sample.

Procedure

The procedure was approved by the Institutional Review Board at the University of Illinois Urbana-Champaign, and all participants provided written informed consent before participating in study procedures. Participants initially underwent the cognitive assessments, followed by the physical function assessments. The order of tests was standardized and participants were provided seated-rest between the administrations of the physical function assessments. Participants were then instructed to wear the accelerometer during waking hours and document wear time in a log book for a seven-day period after the testing session. Participants received $50 for completing the measures in the laboratory and $25 for wearing and returning the accelerometer.

Data Analysis

Data were analyzed in SPSS Statistics Version 24 (IBM Corporation, Armonk, NY). To address the first hypothesis, group differences (i.e., older adults with MS vs. controls) in physical and cognitive function variables were examined using independent samples *t*-tests with the differences between groups expressed using Cohen's *d* (difference in mean scores divided by the pooled SD) with values of 0.2, 0.5, and 0.8 representing small, moderate, and large differences, respectively (Cohen, 1988). To address the second hypothesis, group differences (i.e., older

adults with MS vs. controls) in physical activity and sedentary behavior variables were examined using analysis of covariance (ANCOVA) with condition (Group: MS or Control) as the between subjects factor and accelerometer wear time (minutes) as the covariate. Effect sizes for the *F*-statistic were also expressed using Cohen's *d* with values of 0.2, 0.5, and 0.8 representing small, moderate, and large differences, respectively (Cohen, 1988). To address the third hypothesis, partial Pearson correlations (*pr*), controlling for accelerometer wear time, were conducted among physical and cognitive function variables, physical activity, and sedentary behavior. Values for correlation coefficients of 0.1, 0.3, and 0.5 were interpreted as weak, moderate, and strong, respectively (Cohen, 1988). To further examine if physical activity and/or sedentary behavior account for any differences between older adults with MS vs. healthy controls on function outcomes, a hierarchal linear regression was performed. This was undertaken by regressing physical and cognitive function variables on group (i.e., older adults with MS vs. healthy controls) in Step 1 and then adding physical activity and sedentary behavior variables in Step 2. The β-coefficients for physical and cognitive function variables were compared between Step 1 and Step 2 to examine if physical activity and/or sedentary behavior accounted for the differences between group (i.e., older adults with MS and healthy controls).

Chapter 4:

Results

Participant Characteristics

Demographic and clinical characteristics of the sample are presented in Table 1. Briefly, the mean (SD) age for older adults with MS and controls were similar (65.3 (4.3) and 66.5 (6.7), respectively). Both older adults with MS and controls had similar body mass index (28.5 (6.9) and 27.1 (5.0), respectively) and were primarily composed of women (n = 25/40; 62.5%). Older adults with MS had predominantly relapsing-remitting MS (RRMS), a mean (SD) disease duration of 21.5 (8.6) years, and moderate disability based on the median EDSS score (4.0 (IQR = 2.0)).

Physical and Cognitive Function, Physical Activity, and Sedentary Behavior

Descriptive data and statistical analyses of physical and cognitive function, physical activity, and sedentary behavior for older adults with MS and age- and sex-matched healthy controls are presented in Table 2. In regards to physical function, older adults with MS performed significantly worse on all measures compared to controls, with moderate differences for the balance (d = 0.6) and gait speed (d = 0.7) components of the SPPB, and large differences for the T25FW (d = 1.0), 6MW (d = 1.6), TUG (d = 0.9), 6SST (d = 1.0), total SPPB score (d = 1.3), and the chair rises component of the SPPB (d = 1.4). Regarding cognitive function, older adults with MS performed significantly worse on the SDMT (i.e., measure of information processing speed) compared to controls (48.3 (11.2) vs. 55.0 (7.8), respectively) and this effect was moderate in magnitude (d = 0.7). There were no statistically significant differences for the other measures of cognitive function.

Both older adults with MS and controls had similar number of days of valid accelerometer data (i.e., 10 hours of wear time without periods of continuous zeros exceeding 60 minutes indicative of non-compliance). However, wear time (minutes/day) was significantly different between groups, such that older adults with MS wore the accelerometer approximately 50 minutes less per day compared to controls (797.8 (97.8) vs. 851.8 (79.3)), respectively). When controlling for accelerometer wear time (minutes/day), older adults with MS engaged in approximately 23 minutes less MVPA per day compared to controls (12.6 (14.1) vs. 35.7 (23.0)), and this effect was large in magnitude (d = 1.2). Older adults with MS further spent approximately 5 minutes more in sedentary behavior per day compared to controls (539.7 (84.7) vs. 534.4 (81.8)) and this effect was weak in magnitude (d = 0.1). There were no statistically significant differences in LPA (minutes/day) or any patterns of physical activity or sedentary behavior between older adults with MS and controls.

Physical Activity and Physical and Cognitive Function

The associations among physical and cognitive function and physical activity in older adults with MS and age- and sex-matched healthy controls are presented in Table 3. The partial Pearson correlations (pr), controlling for accelerometer wear time (minutes), indicated statistically significant and moderate-to-large associations between LPA (minutes/day) and a majority of physical function variables (e.g., T25FW, 6MW, TUG, 6SST, gait speed and chair rises components of SPPB) in older adults with MS (pr = 0.39−0.54). In controls, LPA (minutes/day) was only significantly associated with total SPPB score (pr = 0.42) and the balance (pr = 0.38) and chair rises (pr = 0.38) components of the SPPB. The partial Pearson correlations further indicated significant and similar associations between MVPA (minutes/day)

and a majority of physical function variables (e.g., T25FW, 6MW, TUG, 6SST, and total SPPB score) in both older adults with MS (*pr* = 0.37−0.59) and controls (*pr* = 0.34−0.55). MVPA was also significantly associated with the gait speed component of the SPPB in older adults with MS (*pr* = 0.42) and the chair rises component of the SPPB in controls (*pr* = 0.46). There were further significant moderate-to-large associations between number of activity bouts/day and all physical function variables, with the exception of the balance component of the SPPB, in older adults with MS (*pr* = 0.39−0.56), but no significant associations in controls. The TUG, 6SST, total SPPB score and gait speed and chair rises components of the SPPB were significantly associated with duration of activity bouts (minutes/day) in older adults with MS (*pr* = 0.33−0.41); there were no significant associations in controls. In regards to cognitive function, the only significant associations were between SDMT and number of activity bouts/day in older adults with MS (*pr* = 0.39) and MVPA (minutes/day) in controls (*pr* = 0.37).

Sedentary Behavior and Physical and Cognitive Function

The associations among physical and cognitive function and sedentary behavior in older adults with MS and age- and sex-matched healthy controls are presented in Table 4. The partial Pearson correlations, controlling for accelerometer wear time (minutes), indicated statistically significant and moderate associations between sedentary behavior (minutes/day) and two physical function variables in older adults with MS, including the 6MW (*pr* = -0.33) and the TUG (*pr* = 0.33); there were no significant associations in controls. The partial Pearson correlations also indicated significant and moderate associations between the duration of sedentary bouts (minutes) and all physical function variables, with the exception of the balance component of the SPPB, in older adults with MS (*pr* = 0.39−0.49), but no significant

associations in controls. There were significant and moderate associations between the number of long (≥30 minutes) sedentary bouts/day and physical function variables in older adults with MS (e.g., T25FW, 6MW, TUG, 6SST, and the gait speed and chair rises components of the SPPB; *pr* = 0.33−0.40) and in controls (e.g., total SPPB score (*pr* = -0.35) and the balance component of the SPPB (*pr* = -0.38). The partial Pearson correlations further indicated significant and moderate-to-large associations between the duration of long sedentary bouts (minutes) and all physical function variables, with the exception of the balance component of the SPPB, in older adults with MS (*pr* = 0.44−0.62), but no significant associations in controls. There was one significant association between number of sedentary bouts/day and the balance component of the SPPB in older adults with MS (*pr* = 0.36) but no significant associations in controls. There were no significant associations between any of the cognitive function variables and sedentary behavior measures.

Linear Regression

All physical and cognitive function variables that were significantly different between older adults with MS and controls (i.e., T25FW, 6MW, TUG, 6SST, SPPB, and SDMT) were regressed on sedentary behavior and MVPA (minutes/day). The regression analyses indicated that MVPA (minutes/day) partially accounted for the effect of group (older adults with MS vs. controls) on the significantly different physical and cognitive function variables (Table 5). However, sedentary behavior (minutes/day) did not make any contribution beyond MVPA in explaining group differences in physical and cognitive function. For example, when the 6MW was regressed on Group in Step 1, the β-coefficient was statistically significant (β = -0.64, p < 0.05); when MVPA (minutes/day) was added in Step 2, the β-coefficient become attenuated, but

still significant (β = -0.40, $p < 0.05$). However, when sedentary behavior (minutes/day) was also added in Step 2, the β-coefficient remained the same. When the SDMT was regressed on Group in Step 1, the β-coefficient was statistically significant ($\beta = -0.32$, $p < 0.05$); when MVPA (minutes/day) was added in Step 2, the β-coefficient become attenuated and no longer statistically significant (β = -0.17, $p = 0.17$). Further, when sedentary behavior (minutes/day) was also added in Step 2, the β-coefficient remained the same.

Chapter 5:

Discussion

The current study examined physical and cognitive function in older adults with MS (i.e., 60 years of age and older) compared to age- and sex-matched healthy older adults in the general population and the extent to which objectively measured physical activity and sedentary behavior were associated with these functions. The primary results of the present study were: (a) older adults with MS demonstrated greater impairments in all measures of physical function compared to healthy controls, including the T25FW, 6MW, TUG, 6SST, total SPPB score and components (i.e., balance, gait speed, and chair rises); (b) older adults with MS only demonstrated greater impairment in one measure of cognitive function compared to healthy controls (i.e., the SDMT as a measure of information processing speed); (c) older adults with MS engaged in less MVPA (minutes) per day and more sedentary behavior (minutes) per day compared to healthy controls with no differences in patterns of physical activity (i.e., activity bouts), LPA (minutes/day), or patterns of sedentary behavior (i.e., sedentary bouts); (d) physical activity, specifically minutes/day of LPA and MVPA, and the number and duration of activity bouts/day were significantly associated with a majority of physical function variables but not cognitive function variables in both older adults with MS and healthy controls but to a greater extent in older adults with MS; (e) sedentary behavior, specifically the duration of sedentary bouts (minutes), number of long (≥30 minutes) sedentary bouts/day and the duration of long sedentary bouts (minutes) were significantly associated with a majority of physical function variables but not cognitive function variables primarily in older adults with MS; and (f) MVPA (minutes/day), but not sedentary behavior (minutes/day) partially explained the differences in physical and cognitive function between older adults with MS and healthy controls.

The result that older adults with MS demonstrate greater impairments in all objective measures of physical function compared to healthy controls is largely in agreement with previous research (Minden et al., 2004). Importantly, all measures demonstrated either moderate (e.g. balance and gait speed components of the SPPB) or large differences (e.g., T25FW, 6MW, TUG, 6SST, total SPPB score, and chair rises component of the SPPB) between older adults and healthy controls based on effect size (*d*). Regarding the T25FW, older adults with MS completed the assessment in 7.9 (5.4) seconds, and previous research demonstrated that a T25FW time of 6.0 to 7.99 seconds was associated with occupational disability and needing "some help" with instrumental activities of daily living in a sample of 159 middle-aged adults with MS (Goldman et al., 2013). Further, a previous systematic review of factors associated with falls in persons with multiple sclerosis demonstrated a mean T25FW time ranged from 6.9 to 8.4 seconds and from 5.8 to 6.9 seconds in fallers and non-fallers, respectively, according to four different studies (standard mean difference (SMD) = 0.45; 95% CI = 0.20−0.70, $p < 0.0005$) (Gianni et al., 2014). This same review further demonstrated mean TUG scores ranged from 2.7 to 12.5 seconds and from 2.5 to 11.4 seconds in fallers and non-fallers, respectively, according to three different studies (SMD = 0.31; 95% CI = 0.01−0.60, $p = 0.04$) (Gianni et al., 2014). The current sample of older adults had a mean (SD) TUG time of 12.6 (10.0) seconds, compared to 6.0 (1.2) seconds in healthy controls ($d = 4.1$). Therefore, the current sample of older adults with MS may be at an increased risk of falling as falls are very common in persons with MS. For the SPPB, the mean (SD) total score of 9.0 (2.5) and component scores (i.e., balance: 3.5 (0.9), gait speed: 3.5 (1.0), and chair rises: 2.0 (1.3) in older adults with MS were similar to scores previously reported in a sample of 48 older adults with MS (59.5 (5.8) years of age; Motl et al., 2015). Further, the mean total SPPB score of 9.0 in the current sample of older adults with MS was below the cut-off

value of 10.0, indicating elevated risk for developing future disability (Guralnik et al., 2000). Of note, the lower extremity strength (i.e., chair rises) component of the SPPB demonstrated the largest decrement in physical function in older adults with MS compared to healthy controls.

In contrast to the measures of physical function, older adults performed worse in only one measure of cognitive function (i.e., the SDMT as a measure of information processing speed) compared to healthy controls. The mean (SD) score of 48.3 (11.2) on the SDMT in older adults with MS was ~7 points less than the mean (SD) score of 55.0 (7.8) in healthy controls. Further, the mean SDMT scores for older adults with MS and healthy controls was 0.18 SD-units below and 0.60 SD-units above the regression-based normative value (controlled for age, sex, and education), respectively. Therefore, both older adults with MS and healthy controls, on average, were not cognitively impaired (> 1.5 SD-units below the regression-based normative value) (Parmenter et al., 2009). This result is similar to a previous study that demonstrated older adults with MS (59–74 years of age) performed worse on a different measure of information processing speed (i.e., Stroop Color and Word Naming Tests) compared to healthy age- and sex-matched controls (Bodling et al., 2009). However, as older adults with MS performed worse than healthy controls on only one measure of cognitive function compared to all measures of physical function, older adults with MS may be at a higher risk of motor dysfunction compared to cognitive dysfunction. Our results supplement a recent study that demonstrated the aging process may affect physical and cognitive function differently in persons with MS (Roy et al., 2016). Previous research has identified hypotheses for this discrepancy in worsened physical and cognitive function in older adults with MS, such as pathological changes specifically impacting physical function as well as the influence of cognitive reserve (Sanai et al., 2010; Roy et al., 2016); however, the underlying cause is still ambiguous.

Importantly, the results of the current study further suggest that physical activity, namely MVPA (minutes/day), might partially influence the magnitude of differences in both physical and cognitive function between older adults with MS and healthy controls. Previous research demonstrated that older adults with MS engage in less MVPA and more sedentary behavior per day compared to young and middle-aged adults with MS (Klaren et al., 2016); however, the current study is novel in that older adults with MS also engaged in less MVPA (minutes) per day and more sedentary behavior (minutes) per day compared to age- and sex-matched healthy controls. The difference in MVPA between older adults with MS and healthy controls was quite large, whereas the difference in sedentary behavior was rather small. The older adults with MS engaged in 12.6 (14.1) minutes of MVPA/day whereas healthy controls engaged in 35.7 (23.0) minutes of MVPA/day (d = 1.2). The current results demonstrate that older adults with MS, on average, are not meeting the public health guidelines for MVPA (i.e., ≥30 minutes/day of MVPA) and therefore are not reaping the public health benefits of physical activity.

Older adults with MS further engaged in 539.7 (84.7) minutes of sedentary behavior/day whereas healthy controls engaged in 534.4 (81.8) minutes (d = 0.1). These results agree with a recent meta-analysis that demonstrated persons with MS are less physically active than non-diseased populations (effect size (ES) = -0.57, 95% CI = -0.76−-0.37; Kinnett-Hopkins et al., 2017). There were no statistically significant differences in patterns of physical activity (i.e., activity bouts), LPA (minutes/day), or patterns of sedentary behavior (i.e., sedentary bouts). Further, when the physical and cognitive function variables were regressed on MVPA and sedentary behavior (minutes/day), only MVPA partially contributed to the differences between older adults with MS and healthy controls on physical and cognitive function. Therefore, these results highlight the need for behavioral interventions in older adults with MS to largely focus on

increasing MVPA as well as decreasing sedentary behavior, with the overall goal of managing the progression and consequences of the disease, including impairments in physical and cognitive function.

Physical activity, specifically minutes/day of LPA and MVPA, and the number and duration of activity bouts/day were significantly associated with most physical function variables in both older adults with MS and healthy controls, but to a greater extent in older adults with MS. This result is somewhat surprising as much previous research has demonstrated physical activity to be associated with physical function in healthy older adults (Taylor et al., 2004) and in older adults with chronic diseases (de Vries et al., 2012). While there were few associations among minutes/day of LPA and MVPA and physical function variables in the healthy controls, there were no associations among patterns of physical activity (i.e., number or duration of activity bouts/day) and physical function. By comparison, both levels (i.e., minutes/day of LPA and MVPA) and patterns (i.e., number or duration of activity bouts/day) of physical activity were associated with almost all physical function variables in older adults with MS. Perhaps there is more opportunity for associations in older adults with MS as older adults with MS have greater impairments in physical function compared to healthy controls; therefore, there is less of a ceiling effect for associations with physical activity in older adults with MS. Regarding the cognitive function variables, there were only two significant associations between SDMT and minutes/day of MVPA in healthy controls and SDMT and number of activity bouts/day in older adults with MS. This result is very unexpected and contradicts previous research that demonstrated associations between physical activity and cognitive function in adults with MS (Morrison & Mayer, 2016) and in healthy older adults in the general population (Bherer et al., 2013). Overall, these results are novel and suggest that behavioral interventions in older adults

with MS should not only focus on increasing levels of both LPA and MVPA, but also on activity bouts throughout the day, as means for potentially improving physical function.

Sedentary behavior, specifically the duration of sedentary bouts (minutes), number of long (≥30 minutes) sedentary bouts/day, and the duration of long sedentary bouts (minutes) were significantly associated with many physical function variables but not cognitive function variables primarily in older adults with MS. The lack of associations among sedentary behavior and physical and cognitive function in healthy controls is again surprising as previous research has demonstrated sedentary time to be strongly associated with diminished physical (Seguin et al., 2012) and cognitive (Vance et al., 2005) function in healthy older adults. The associations between sedentary behavior and physical function in older adults with MS, however, is much in agreement with previous research. For example, one study demonstrated that greater sedentary time (minutes/day) was significantly correlated with lower 6MW distance and slower T25FW in middle-aged adults with MS (Hubbard & Motl, 2015). The current study is novel in that patterns of sedentary behavior (i.e., sedentary bouts) were also moderately associated with physical function and support the notion that transitions from sedentary to non-sedentary behavior are important for physical function in addition to cardiometabolic health (Healy et al., 2011). The lack of associations among sedentary behavior and cognitive function in older adults with MS is similar to a previous study that also demonstrated no associations between sedentary behavior (minutes/day) and cognitive function (i.e., SDMT performance) in middle-aged adults with MS (Hubbard & Motl, 2015). However, there is very limited research on sedentary behavior in older adults in the general population as well as older adults with MS that warrants continued research on prospective associations with physical and cognitive function.

The current study involved a relatively large sample size, direct comparisons of older adults with MS and age- and sex-matched healthy controls, and objective and comprehensive measurements of sedentary behavior, physical activity, and physical and cognitive function. However, there are several limitations. Firstly, this study utilized a cross-sectional research design and therefore the results of this study only suggest correlations among sedentary behavior, physical activity, and function but no determination of causation. The results cannot determine whether sedentary behavior and physical activity influence physical and cognitive function or vice versa. The current sample of older adults with MS and healthy controls were relatively young (65.3 (4.3) and 66.5 (6.7) years of age, respectively) and perhaps the results may not be fully generalized to older adults greater than 65−70 years of age. Further, the majority of the sample of older adults with MS had mild-to-moderate disability (i.e., EDSS score 3.5−5.5; 60%) and therefore the current results may also not be generalized to older adults with higher levels of disability. Lastly, the current study did not include other measures that may have affected the associations of sedentary behavior, physical activity, and physical and cognitive function, such as fatigue, which is highly prevalent in persons with MS (Bakshi, 2003).

Chapter 6:

Conclusions

The current study demonstrated older adults with MS (i.e., 60 years of age and older) had greater impairments in many areas of physical function (i.e., walking speed and endurance and lower extremity strength) but only one area of cognitive function (i.e., information processing speed) compared to age- and sex-matched healthy controls. Older adults with MS further engaged in lower levels of MVPA (minutes/day) and higher levels of sedentary behavior (minutes/day) compared to healthy controls. Both levels and patterns of physical activity and sedentary behavior were associated with physical function to a greater extent in older adults with MS compared to healthy controls. Importantly, the low levels of MVPA in older adults with MS partially contributed to the differences in physical and cognitive function. Overall, such results identify a large decline in physical function, but not cognitive function in older adults with MS compared to healthy controls, and that both levels and patterns of physical activity and sedentary behavior should be an emphasis of clinical rehabilitation and behavioral interventions for the promotion of healthy aging in older adults with MS.

Chapter 7:

Figure and Tables

Figure 1. Mechanisms of aging and MS on physical and cognitive function and the potential effects of physical activity and sedentary behavior.

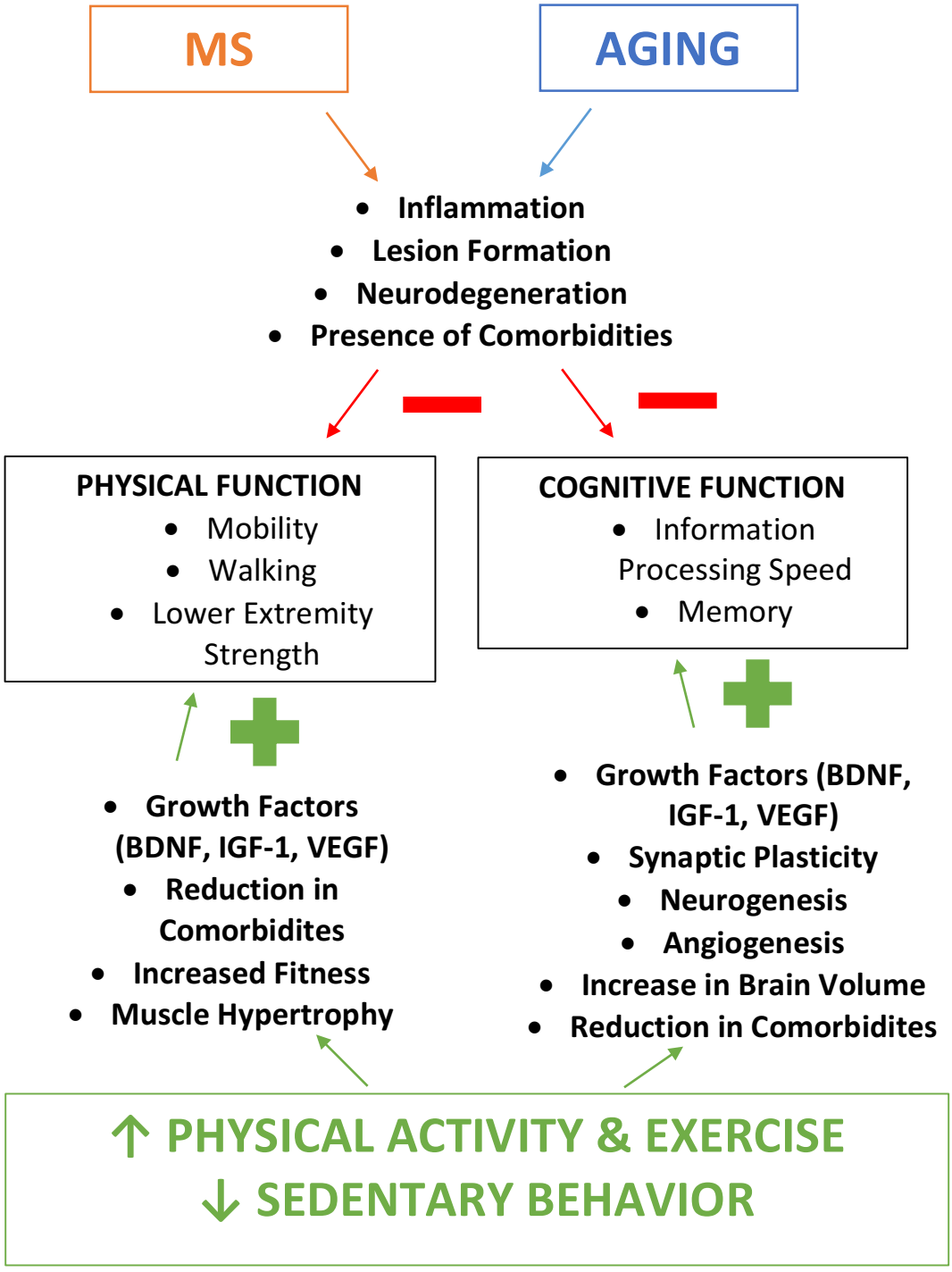

Table 1. Demographic and clinical characteristics of the older adults with MS and age- and sex-matched healthy controls

Variable	MS (n=40)	Controls (n=40)
Age, years	65.3 (4.3)	66.5 (6.7)
Sex, % female (n=)	62.5 (n=25)	62.5 (n=25)
BMI (kg/m^2)	28.5 (6.9)	27.1 (5.0)
MS Type, % RRMS	67.5	
EDSS score (mdn, IQR)	4.0 (2.0)	
0−3.0 (n=, %)	8 (20.0)	
3.5−5.5 (n=, %)	24 (60.0)	
6−8.0 (n=, %)	8 (20.0)	
MS Duration, years	21.5 (8.6)	
AD Use, %	25.0	0.0

Note. Data presented as mean (SD), unless otherwise noted. MS=multiple sclerosis; BMI=body mass index; RRMS=relapsing-remitting MS; EDSS=Expanded Disability Status Scale; AD=assistive device

Table 2. Descriptive characteristics and statistical analyses of physical and cognitive function and physical activity and sedentary behavior in older adults with MS and age- and sex-matched healthy controls

Variable	MS (n=40)	Controls (n=40)	*t*-value	*d*-value
Physical Function				
T25FW, seconds	7.9 (5.4)	4.3 (0.6)	**4.3***	1.0
6MW, feet	1318.8 (447.0)	1938.0 (291.7)	**7.3***	1.6
TUG, seconds	12.6 (10.0)	6.0 (1.2)	**4.1***	0.9
6SST, seconds	14.6 (11.2)	6.8 (1.4)	**4.3***	1.0
SPPB	9.0 (2.5)	11.4 (1.0)	**5.8***	1.3
Balance	3.5 (0.9)	3.9 (0.4)	**2.6***	0.6
Gait Speed	3.5 (1.0)	4.0 (0.2)	**3.2***	0.7
Chair Rises	2.0 (1.3)	3.5 (0.7)	**6.4***	1.4
Cognitive Function				
SDMT	48.3 (11.2)	55.0 (7.8)	**3.1***	0.7
CVLT-II	49.9 (11.5)	52.5 (8.8)	1.2	0.3
BVMT-R	18.5 (7.0)	19.6 (5.9)	0.8	0.2
PASAT	41.2 (12.4)	43.7 (11.6)	0.9	0.2
Accelerometry				
Number of valid days	5.9 (1.7)	6.5 (1.1)	2.0	0.4
Wear time, minutes	797.8 (97.8)	851.8 (79.3)	**2.7***	0.6
	MS (n=40)	**Controls (n=40)**	***F*-value**	***d*-value**
Physical Activity				
LPA, minutes/day	245.5 (76.5)	281.6 (70.3)	0.9	0.5
MVPA, minutes/day	12.6 (14.1)	35.7 (23.0)	**20.5***	1.2
Number of activity bouts/day	12.4 (4.9)	13.4 (3.7)	0.02	0.2
Duration of activity bouts, minutes	45.9 (29.5)	43.4 (28.2)	0.03	0.1
Sedentary Behavior				
Sedentary behavior, minutes/day	539.7 (84.7)	534.4 (81.8)	**4.3***	0.1
Number of sedentary bouts	15.2 (3.2)	15.7 (3.1)	0.5	0.2
Duration of sedentary bouts, minutes	24.5 (7.3)	22.9 (3.9)	0.7	0.3
Number of long (≥30 minutes) sedentary bouts	5.9 (1.4)	5.5 (1.9)	2.8	0.2
Duration of long sedentary bouts, minutes	51.4 (8.2)	47.8 (6.0)	2.9	0.5

Note. Data presented as mean (SD). *Denotes statistical significance, $p<0.05$. MS=multiple sclerosis; T25FW=Timed 25-Foot Walk; 6MW=Six-Minute Walk; TUG=Timed Up-and-Go; 6SST=Six-Spot Step Test; SPPB=Short Physical Performance Battery; SDMT=Symbol Digit Modalities Test; CVLT-II=California Verbal Learning Test-II; BVMT-R=Brief Visuospatial Memory Test-Revised; PASAT=Paced Auditory Serial Addition Test; LPA=light physical activity; MVPA=moderate-to-vigorous physical activity

Table 3. Correlations among physical activity and physical and cognitive function in older adults with MS (n=40) and age- and sex-matched healthy controls (n=40)

Variable	Physical Activity			
	LPA, minutes/day	MVPA, minutes/day	Number of activity bouts/day	Duration of activity bouts, minutes/day
Physical Function				
T25FW, seconds	**-0.53***, -0.14	**-0.39***, **-0.34***	**-0.54***, 0.17	-0.27, -0.02
6MW, feet	**0.42***, 0.13	**0.59***, **0.55***	**0.39***, -0.07	0.18, -0.08
TUG, seconds	**-0.52***, -0.30	**-0.37***, **-0.48***	**-0.63***, 0.04	**-0.38***, 0.09
6SST, seconds	**-0.54***, -0.14	**-0.39***, **-0.43***	**-0.60***, -0.10	**-0.34***, -0.20
SPPB	**0.39***, **0.42***	**0.42***, **0.44***	**0.56***, -0.12	**0.34***, -0.12
Balance	-0.09, **0.38***	0.29, 0.26	0.22, -0.17	-0.04, -0.03
Gait Speed	**0.47***, 0.04	**0.42***, 0.05	**0.55***, -0.24	**0.33***, -0.03
Chair Rises	**0.44*, 0.38***	0.27, **0.46***	**0.50***, -0.03	**0.41***, -0.14
Cognitive Function				
SDMT	0.19, 0.28	0.21, **0.37***	**0.40***, 0.01	0.21, -0.21
CVLT-II	-0.08, 0.13	0.02, 0.03	0.07, -0.18	-0.01, -0.01
BVMT-R	0.06, 0.04	0.17, 0.10	0.09, -0.18	0.20, -0.06
PASAT	-0.02, 0.07	0.27, 0.15	0.29, -0.21	0.12, -0.06

Note. Partial Pearson product-moment correlations (*pr*), controlling for accelerometer wear time (minutes). *Denotes statistical significance, $p<0.05$. Data presented as MS, controls. MS=multiple sclerosis; T25FW=Timed 25-Foot Walk; 6MW=Six-Minute Walk; TUG=Timed Up-and-Go; 6SST=Six-Spot Step Test; SPPB=Short Physical Performance Battery; SDMT=Symbol Digit Modalities Test; CVLT-II=California Verbal Learning Test-II; BVMT-R=Brief Visuospatial Memory Test-Revised; PASAT=Paced Auditory Serial Addition Test; LPA=light physical activity; MVPA=moderate-to-vigorous physical activity

Table 4. Correlations among sedentary behavior and physical and cognitive function in older adults with MS (n=40) and age- and sex-matched healthy controls (n=40)

Variable	Sedentary Behavior				
	Sedentary behavior, minutes/day	Number of sedentary bouts	Duration of sedentary bouts, minutes	Number of long (≥30 minutes) sedentary bouts	Duration of long sedentary bouts, minutes
Physical Function					
T25FW, seconds	0.29, 0.10	-0.06, 0.11	**0.49***, -0.07	**0.37***, 0.06	**0.56***, 0.01
6MW, feet	**-0.33***, -0.03	-0.01, -0.09	**-0.45***, 0.20	**-0.37***, 0.03	**-0.56***, 0.10
TUG, seconds	**0.33***, 0.14	-0.01, 0.09	**0.48***, 0.06	**0.42***, 0.10	**0.51***, 0.20
6SST, seconds	0.31, 0.03	-0.02, 0.06	**0.49***, -0.11	**0.40***, -0.07	**0.56***, 0.09
SPPB	-0.18, -0.24	0.14, -0.27	**-0.45***, -0.07	-0.31, **-0.35***	**-0.56***, 0.02
Balance	0.18, -0.26	**0.36***, -0.23	-0.23, -0.12	0.07, **-0.38***	-0.17, -0.02
Gait Speed	-0.25, -0.14	0.04, -0.20	**-0.39***, 0.02	**-0.33***, -0.15	**-0.44***, 0.01
Chair Rises	-0.28, -0.17	-0.01, -0.21	**-0.39***, -0.04	**-0.37***, -0.26	**-0.62***, 0.03
Cognitive Function					
SDMT	0.01, -0.08	0.09, -0.12	-0.22, -0.11	-0.17, -0.08	-0.05, -0.21
CVLT-II	0.30, -0.08	0.24, -0.17	0.01, -0.10	0.22, -0.27	0.04, -0.02
BVMT-R	-0.03, 0.05	0.08, -0.04	-0.08, 0.10	-0.02, 0.02	-0.02, 0.11
PASAT	0.14, -0.08	0.20, -0.08	-0.18, 0.01	0.03, -0.09	0.08, -0.01

Note. Partial Pearson product-moment correlations (*pr*), controlling for accelerometer wear time (minutes). *Denotes statistical significance, $p<0.05$. Data presented as MS, controls.
MS=multiple sclerosis; T25FW=Timed 25-Foot Walk; 6MW=Six-Minute Walk; TUG=Timed Up-and-Go; 6SST=Six-Spot Step Test; SPPB=Short Physical Performance Battery; SDMT=Symbol Digit Modalities Test; CVLT-II=California Verbal Learning Test-II; BVMT-R=Brief Visuospatial Memory Test-Revised; PASAT=Paced Auditory Serial Addition Test

Table 5. Summary of linear regression analyses of physical and cognitive function and MVPA in older adults with MS (n=40) and age- and sex-matched healthy controls (n=40)

	T25FW, seconds		6MW, feet		TUG, seconds	
Variable	**B (SE B)**	**β**	**B (SE B)**	**β**	**B (SE B)**	**β**
Step 1 (Group)	3.66 (0.87)	0.43*	-616.84 (85.80)	-0.64*	6.63 (1.61)	0.43*
Step 2a (Group)	2.58 (1.0)	0.31*	-383.87 (86.35)	-0.40*	4.57 (1.84)	0.29*
Step 2b (MVPA (minutes/day))	-0.05 (0.02)	-0.25*	10.19 (1.95)	0.47*	-0.09 (0.04)	-0.25*
	6SST, seconds		**SPPB**		**SPPB Balance**	
	B (SE B)	**β**	**B (SE B)**	**β**	**B (SE B)**	**β**
Step 1 (Group)	7.77 (1.80)	0.44*	-2.45	-0.55*	-0.41	-0.29*
Step 2a (Group)	5.37 (2.06)	0.31*	-1.67	-0.37*		
Step 2b (MVPA (minutes/day))	-0.10 (0.05)	-0.26*	0.03	0.33*		
	SPPB Gait Speed		**SPPB Chair Rises**		**SDMT**	
	B (SE B)	**β**	**B (SE B)**	**β**	**B (SE B)**	**β**
Step 1 (Group)	-0.54	-0.35*	-1.50	-0.58*	-6.54	-0.32*
Step 2a (Group)			-1.10	-0.42*	-3.41	-0.17
Step 2b (MVPA (minutes/day))			0.02	0.30*	0.14	0.30*

Note. *Denotes statistical significance, $p<0.05$. MS=multiple sclerosis; T25FW=Timed 25-Foot Walk; 6MW=Six-Minute Walk; TUG=Timed Up-and-Go; 6SST=Six-Spot Step Test; SPPB=Short Physical Performance Battery; SDMT=Symbol Digit Modalities Test

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