FITNESS AND COGNITIVE PROCESSING SPEED IN PERSONS WITH MULTIPLE SCLEROSIS

BY

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THESIS

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Abstract

Background: Cognitive impairment is prevalent, disabling, and poorly managed in persons with MS. To date, two studies have identified aerobic capacity as a correlate of cognition in MS, but there has yet to be an investigation of multiple domains of fitness as correlates of cognition in this population. Such an examination is important for identifying the appropriate modes of exercise training for possibly improving cognition.

Objective: This study examined the relationships among aerobic capacity, muscle strength, and balance with cognitive function in persons with MS.

Methods: 31 persons with MS and 31 controls matched by age, height, weight, and sex completed two neuropsychological measures of cognitive processing speed (PASAT and SDMT). Participants underwent an incremental exercise test to exhaustion on a cycle ergometer as a measure of aerobic capacity; three maximal isometric extensions and one maximal isometric flexion with each knee on an isokinetic dynamometer at three different joint angles as a measure of muscular strength; and stood on a force platform without shoes for 30 seconds with eyes open to measure postural sway.

Results: Independent samples *t*-tests indicated that MS and control groups differed in PASAT score ($t = -2.13$, $p = .04$), SDMT score ($t = -2.69$, $p = .01$), aerobic capacity ($t = -2.99$, $p < .01$), and balance ($t = 4.06$, $p < .01$), but not in muscular strength. Cognitive processing speed was significantly associated with aerobic capacity ($r = .43$ and $.44$) and balance ($r = -.52$ and $-.52$), but not muscular strength in the overall and MS samples, respectively. Lastly, hierarchical

regression analysis indicated that aerobic capacity (β = .27) and balance (β = −.40) accounted for differences in cognitive processing speed between MS and control groups.

Conclusions: Aerobic capacity and balance, but not muscular strength, are associated with cognitive processing speed in persons with MS, suggesting that aerobic exercise and balance training are avenues for possibly improving cognitive impairment in this population.

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Chapter 1—Introduction

Multiple sclerosis (MS) can be described as a non-traumatic neurodegenerative disease with an estimated prevalence of 1 per 1000 people in the United States (Mayr, et al., 2003; Wallin, Page, & Kurtzke, 2000). This disease is initially characterized by immune-mediated, multi-focal demyelination in white matter of the brain and spinal cord (Mitchell, Benito-Leon, Gonzalez, & Rivera Navarro, 2005; Trapp & Nave, 2008). The disease process eventually causes damage of both grey and white matter in the brain, resulting in the accumulation of both physical and cognitive disability.

There is increasing evidence that cognitive impairment is prevalent and poorly managed in persons with MS. In studies involving neuropsychological testing, an estimated 45-65% of individuals with MS experience cognitive impairment as a prominent symptom (Bobholz & Rao, 2003; Prakash et al., 2007). This impairment is often seen in domains of working memory, processing speed, and executive control (Prakash et al., 2007). There is no FDA-approved treatment for cognitive impairment in MS, and trials of pharmacological agents (e.g. modafinil, L-amphetamine, donepezil) as well as studies involving cognitive rehabilitation generally have been conflicting and disappointing (Amato, Portaccio & Zipoli, 2006; Morrow et al., 2009; Stankoff et al., 2005).

Exercise training might represent a behavioral approach for managing cognitive dysfunction in MS. This is based on emerging interest by researchers and clinicians in the effects of fitness (i.e., characteristics of an individual reflecting aerobic capacity, muscular strength, balance, agility, etc.) and exercise (i.e., planned behavior aimed towards improving an individual's fitness) on cognition in persons with MS (Motl, Sandroff, & Benedict, 2011).

Indeed, two studies have examined cardiorespiratory fitness (a presumed surrogate of aerobic exercise training) as a correlate of cognitive function in MS (Prakash et al., 2007; 2010), and two studies have examined the effects of exercise training on cognition (Oken et al., 2004; Romberg, Virtanen & Ruutiainen, 2005). Cardiorespiratory fitness, in one study, was associated with faster reaction times on the PVSAT (a valid measure of sustained attention, processing speed, and working memory in persons with MS), greater activation of the right inferior frontal gyrus and middle frontal gyrus (regions of the cerebral cortex), and less activation of the anterior cingulate cortex (Prakash, 2007). The other study reported that cardiorespiratory fitness was positively associated with both white and grey matter integrity and processing speed in persons with MS and healthy controls (Prakash, 2010). By comparison, neither aerobic exercise training, resistance exercise training, nor yoga improved cognition in MS (Oken et al., 2004; Romberg, 2005). Such null results from the training studies highlight the importance of considering the well-established gerontological literature (Hillman, Erickson, & Kramer, 2008) as a way of better informing examinations of fitness, exercise training, and cognition in MS.

Fitness and exercise training have been associated with better cognitive performance in older adults (a population who commonly experiences cognitive decline). One meta-analysis reported that exercise training was associated with overall better performance on cognitive tasks with an average effect size of 0.478 standard deviations (Colcombe & Kramer, 2003). Interestingly, the moderator analysis indicated that combined exercise training (both strength and aerobic training) was associated with greater improvements in cognition than aerobic training alone (Colcombe, 2003). Other studies have reported that cardiorespiratory fitness, muscle strength, and balance, respectively, are associated with better cognitive function in older adults (Newson & Kemps, 2008; Boyle et al., 2009; Voelcker-Rehage, Godde, & Staudinger, 2010).

This would suggest that cardiorespiratory fitness, muscle strength, and balance have the potential for independent contributions towards combating cognitive impairment in older adults and perhaps MS.

The gerontology literature provides a backdrop for the current study of fitness and cognition in MS by indicating that different types of fitness and modes of training are important when developing interventions to maximize cognitive benefits. The purpose of this study, therefore, was to examine the relationships among cardiorespiratory fitness, muscle strength, and balance as components of fitness and cognitive function in MS. This examination of fitness will inform the development of subsequent exercise training interventions aimed at improving cognition in individuals with MS. First, we examined group differences in fitness and cognition among persons with MS and healthy controls; we then evaluated which domains of fitness were associated with cognition in the overall, MS, and control samples, separately; and finally, we examined fitness as a mediator of group differences in cognition and identified the independent contributions of fitness variables for explaining such differences in cognition. Accordingly, the first hypothesis was that there would be significant differences in fitness and cognition between persons with MS and healthy controls. The second hypothesis was that cardiorespiratory fitness, muscular strength, and balance would each be associated with cognition in persons with MS, and that cardiorespiratory fitness would have the strongest association, based on findings from the gerontology literature. The third hypothesis was that all three domains of physical fitness would explain group differences in cognition between persons with MS and healthy controls (i.e., mediation).

Chapter 2—Review of Literature

EPIDEMIOLOGY OF MULTIPLE SCLEROSIS

Multiple sclerosis (MS) can be described as a non-traumatic neurodegenerative disease that typically presents in the 3rd or 4th decade of life (Wallin, Page, & Kurtzke, 2000; Mayr et al., 2003). As of the year 2000, median age of diagnosis was reported to be 37.2 years (Mayr, 2003). Median survival has been reported as between 30-43 years following diagnosis of MS (Wallin, 2000). In terms of sex differences, women are affected nearly three times more often than men (Noonan, Kathman, & White, 2002). Global incidence of MS peaks at about 30 years of age (Koch-Henriksen & Sorenson, 2010), and raw incidence rates have been reported to range from 0.86 per 100,000 person-years to 12.2 per 100,000 person-years (Mayr, 2003).

According to a systematic review of epidemiological studies across the globe (Koch-Henriksen, 2010), MS has been reported to have the highest prevalence estimates in Western Europe and North America, followed by areas in Central and Eastern Europe, the Balkans, and Australia/New Zealand. Regions with the lowest prevalence estimates included Asia, the Middle East, and Africa (Koch-Henriksen, 2010). Accordingly, MS is more common in individuals with northern European ancestry than those with Hispanic, African, or Asian descent (Williamson, 2007; Mayr, 2003). In the United States, multiple sclerosis has an estimated prevalence of 1 per 1000 people (Wallin, 2000; Mayr, 2003; Koch-Henriksen, 2010; Williamson, Henry, Schiffer, & Wagner, 2007; Noonan, 2002). Within the United States, geographically, MS is most prevalent in the northern states with lower prevalence in southern states (Wallin, 2000; Williamson, 2007).

CLINICAL DISEASE COURSE

There are relapsing and progressive presentations of multiple sclerosis. Approximately 85% of those with MS experience a disease course consisting of periodic neurological exacerbations, or relapses, followed by periods of relatively stable neurological function. This biphasic pattern is termed relapsing-remitting multiple sclerosis (RRMS) (Trapp, 2008; Smith & McDonald, 1999; Vollmer, 2007; Mitchell, Benito-Leon, Morales Gonzalez, Rivera-Navarro, 2005). These relapses are attributed to instances of acute inflammation in the central nervous system which cause damage to myelinated axons and neurons (Vollmer, 2007), subsequently hindering neuronal conduction. In the period following this acute inflammation (i.e., remission phase), growth factors promote remyelination of damaged axons in the CNS (Vollmer, 2007; Smith, 1999). These axons undergoing remyelination can regain the ability to conduct, albeit often in a diminished capacity. Over time, the ability for growth factors to remyelinate damaged axons following a relapse decreases, leading to neuronal degeneration and eventual irreversible neurological disability (Vollmer, 2007).

After a period of 8-20 years, a majority of persons with RRMS experience a new disease course consisting of irreversible neurological impairment, termed secondary progressive MS (SPMS) (Trapp, 2008; Smith, 1999; Vollmer, 2007). Additionally, 15% of individuals diagnosed with MS have a disease course that presents with immediate irreversible neurological damage, termed primary progressive MS (PPMS) (Trapp, 2008; Smith, 1999). PPMS is generally later onset than RRMS, and both progressive disease courses have been linked to axonal degeneration (Trapp, 2008; Smith, 1999).

Axonal degradation, which is initially triggered by chronic demyelination associated with progressive MS, leads to irreversible neurological disability (Vollmer, 2007; Trapp, 2008; Smith,

1999). A major goal of treatment for MS is to prevent relapses (i.e., limit chronic demyelination) in order to delay this progression from demyelination to degeneration (Vollmer, 2007). Two mechanisms have been proposed to explain how axonal degeneration occurs in MS. The first mechanism involves axonal degeneration following chronic demyelination due to inadequate trophic support, provided by oligodendrocytes (Trapp, 2008). The other proposed mechanism for this degenerative process is that following chronic demyelination, axons become degenerated due to increases in intracellular calcium (Ca^{2+}), which eventually leads to axonal loss (Trapp, 2008). Recent studies have found that this neurodegeneration occurs in both white and grey matter of the brain and spinal cord (Trapp, 2008; Smith, 1999). Prominent areas of cortical atrophy in the brain include the cingulate gyrus, and insular, frontal, temporal, and parietal cortices, with less degeneration occurring in the primary motor, sensory, and visual cortices (Trapp, 2008).

SYMPTOMS OF MULTIPLE SCLEROSIS

The immune-mediated loss of axons in both white and grey matter in various locations of the brain and spinal cord can lead to a variety of symptoms in individuals with multiple sclerosis. The presentation of symptoms of MS is reflected by the location of lesions in the central nervous system (Lublin, 2007; Vollmer, 2007). The worsening of symptoms over time can occur in either a step-wise (i.e., incomplete recovery from relapses) or a progressive fashion (Lublin, 2007). Initial symptoms of MS often manifest as sensory disturbances, such as Lhermitte's sign, an electrical sensation running down the spine that accompanies neck flexion (Schapiro, 2005; Mitchell, 2005; Smith, 1999). These sensory disturbances often involve lesions of the spinal cord, optic nerve, brainstem, or cerebellum (Lublin, 2007).

Fatigue has been identified as the most common and disabling symptom of MS, and presents as an overwhelming feeling of tiredness during activities of daily life (Schapiro, 2005; Hadjimichael, Vollmer, & Oleen-Burkey, 2008). 74% of persons with MS have reported fatigue to be a prominent symptom of the disease, with 15-40% of individuals reporting fatigue to be the most disabling symptom (Hadjimichael, 2008). Fatigue has been associated with both mobility disability and disease severity (Hadjimichael, 2008). Spasticity, defined as a velocity-dependent stiffness about a joint, is another debilitating symptom of MS (Schapiro, 2005). 53% of persons with MS report experiencing mild to severe spasticity (Rizzo, Hadjimichael, Preiningerova, & Vollmer, 2004). Severe spasticity has been associated with more progressive forms of MS and worse disability (Rizzo, 2004). Many individuals with MS report sensitivity to heat, which is thought to exacerbate axonal conduction block associated with periods of inflammatory demyelination (Smith, 1999). Postural instability and impaired coordination have also been reported as major disturbances in individuals with MS (Schapiro, 2005). Ambulatory impairment is another hallmark symptom of MS associated with decreased quality of life in MS (Pittock et al., 2004), and is a major component of the Expanded Disability Disease Status scale, a clinical measure of disease severity (Pittock, 2004). Optic neuritis has also been associated with multiple sclerosis. 13-85% of patients who experience optic neuritis have been diagnosed with MS (Ebers, 1985). Bladder and bowel dysfunction have been identified as common symptoms of MS as well, with 56% of persons with MS reporting bladder dysfunction and 52% reporting bowel dysfunction (Chia et al., 1995). Finally, psychological disorders have been associated with MS, such as anxiety, depression, and cognitive impairment (Mitchell, 2005).

COGNITIVE DYSFUNCTION IN MS

Cognitive impairment is common and debilitating in multiple sclerosis. In studies involving neuropsychological testing, an estimated 45-65% of individuals with MS experience cognitive impairment as a prominent symptom (Bobholz & Rao, 2003). Cognitive dysfunction is prevalent in the three main disease courses of MS (e.g., RRMS, SPMS, and PPMS), and can often affect individuals in the earliest stages of MS, including clinically isolated syndrome (CIS), even prior to a definite diagnosis of multiple sclerosis (Denney, Sworowski, & Lynch, 2005; Achiron & Barak, 2006). Further, cognitive impairment can affect an individual with MS without the presentation of physical disability (Achiron, 2006; Schulz, Kopp, Kunkel, & Feiss, 2006; Calabrese, 2006). In persons with MS, this dysfunction can negatively impact activities of daily life, such as driving a car (Bobholz, 2003), remembering important information, and multitasking (Mohr & Cox, 2001). Cognitive impairment in individuals with MS has also been associated with unemployment as well as a lack of social support, depression, and increased reliance upon caregivers (Minden & Schiffer, 1990; Mohr, 2001; Bagert, Camplair, & Bourdette, 2002).

Reviews and meta-analyses have documented that cognitive dysfunction, measured by neuropsychological testing, is often seen in domains of working memory, cognitive processing speed, and executive control in persons with MS, but less so in intellectual functions and language skills (Prakash et al., 2007; 2008; Zakzanis, 2000; Bobholz, 2003; Rosti, Hamalainen, Koivisto, & Hokkanen, 2007; Schulz, 2006; Bagert, 2002). In a review conducted by Bobholz and Rao (2003), cross-sectional research indicated that persons with MS performed significantly worse than healthy controls on neuropsychological tests in the domains of working memory, attention, and cognitive processing speed. This trend was observed across a variety of

methodological paradigms for assessing cognition (Bobholz, 2003). Further, persons with progressive MS generally performed worse on neuropsychological batteries than individuals with relapsing-remitting MS (Bobholz, 2003).

Three meta-analyses examined the effects of multiple sclerosis on cognitive function. In a 1997 meta-analysis, Wishart and Sharpe found significant deficits of similar magnitude in all examined domains of cognition in persons with MS. Interestingly, in this quantitative review, disease course was not consistently associated with cognition (Wishart, 1997). Conversely, a later meta-analysis (Zakzanis, 2000) reported that persons with chronic-progressive MS exhibited more impairment in the domain of executive function, whereas individuals with relapsing-remitting MS elicited greater memory impairment. Recently, a third meta-analysis (Prakash et al., 2008) examined cognitive impairments in individuals with RRMS. Overall, diagnosis of RRMS had a negative, moderate size effect on cognition (ES=-0.585) (Prakash, 2008). The domains of executive function and attention (namely cognitive processing speed) and general cognitive ability were more impaired than the domains of verbal functioning and language, concept formation, and reasoning in persons with RRMS (Prakash, 2008).

Many different paradigms of neuropsychological tests have been implemented in order to examine different domains of cognitive function in persons with MS (Bobholz, 2003). As identified in a recent meta-analysis (Prakash et al., 2008), the sub-domain of cognitive processing speed has been of particular interest to researchers and clinicians. Two measures of cognitive processing speed, the Paced Auditory Serial Addition Test (PASAT) and the Symbol Digit Modalities Test (SDMT) have been utilized as screening tools for cognitive dysfunction in persons with MS (Rosti, 2007; Parmenter, Weinstock-Guttman, Garg, Munschauer, & Benedict, 2007). The PASAT is the sole measure of cognition in the Multiple Sclerosis Functional

Composite (Rosti, 2007). One study (Rosti et al., 2007) examined the ability of the PASAT (3.0 second version) to detect cognitive impairment against a comprehensive neuropsychological battery of tests in 45 individuals with RRMS and 48 healthy controls. The PASAT was quite accurate in detecting cognitive deficits in both MS and healthy controls (82% accuracy) as well as in persons with MS alone (74% accuracy) compared with the comprehensive battery of neuropsychological examinations (Rosti, 2007). Another study (Parmenter et al., 2007) examined the effectiveness of the SDMT as a screening tool for cognitive impairment against the MACFIMS battery of neuropsychological tests in 100 individuals with MS and 50 healthy controls. The SDMT classified cognitive dysfunction in persons with MS with 72% accuracy (Parmenter, 2007), a value similar to that of the PASAT (Rosti, 2007).

TREATMENT OF COGNITIVE DYSFUNCTION IN MS

Strategies for specifically treating cognitive impairment in multiple sclerosis have been implemented in two different approaches: pharmacological and non-pharmacological (Amato, Portaccio, & Zipoli, 2006). Currently, there is no FDA-approved treatment for cognitive dysfunction in MS (Amato, 2006). Disease-modifying agents (e.g., interferon beta-1a, interferon beta-1b, and glatiramer acetate) attempt to treat cognitive dysfunction indirectly, by preventing cerebral lesions or reducing cortical atrophy (Amato, 2006). Overall, results from studies linking disease-modifying therapies to performance on neuropsychological tests have been disappointing, primarily due to poor external validity (Amato, 2006).

Additionally, pharmacological symptomatic treatments (e.g., L-amphetamine sulfate, memantine, modafinil, and donepezil) have been utilized to improve cognitive function in individuals with MS to mixed results. L-amphetamine sulfate has been shown to enhance

memory in both animal models and humans (Morrow et al., 2009). In a randomized, double-blind, placebo-controlled trial, a 29-day oral dose of 30 mg of L-amphetamine sulfate (or placebo) was given to 151 individuals with MS who had documented cognitive impairment (Morrow, 2009). Performance on a battery of neuropsychological tests was assessed as a measure of cognition both before and after treatment with L-amphetamine sulfate. Results indicated that there were no significant improvements on subjective ratings of cognition or information processing speed in the L-amphetamine sulfate group (Morrow, 2009).

Memantine, an effective treatment for Alzheimer's disease, was also implemented in a randomized, double-blind, placebo-controlled trial with the aim of improving cognitive dysfunction in persons with MS who had a history of cognitive impairment (Stankoff, 2005). 54 individuals received a titrated 12-week treatment course of memantine and 60 received a placebo over the same duration. A battery of neuropsychological tests was administered both at baseline and completion of the 12-week period as a measurement of cognition (Stankoff, 2005). There were no statistically significant results from any of the cognitive assessments over the duration of memantine therapy.

Modafinil is a pharmacological agent that has also been thought to improve cognitive function in persons with MS (Amato, 2006; Lovera et al., 2010). Modafinil is a stimulant of the central nervous system, and is utilized as a treatment for fatigue in MS (Lovera, 2010). Modafinil has been hypothesized to affect brain regions important in cognition (Lovera, 2010), although there has been no published research on its efficacy for treating cognitive impairment in MS (Amato, 2006).

Recently, donepezil, an acetylcholinesterase inhibitor used to treat dementia in individuals with Alzheimer's disease, has been examined as a potential treatment of cognitive

impairment in MS. In a randomized, double-blind, placebo-controlled study, the effectiveness of donepezil was evaluated in a sample of 69 individuals with MS (Christodoulou et al., 2006). Participants received treatment for 24 weeks with either donepezil or a placebo and completed the Selective Reminding Test (a measure of verbal learning and memory) at both baseline and at the completion of the treatment course (Christodoulou, 2006). Results indicated that patients receiving donepezil significantly improved memory function to a medium effect size compared with the placebo group (Christodoulou, 2006). Results from other studies involving donepezil have been promising; however, more research is needed in larger samples of cognitively impaired individuals with MS (Amato, 2006).

Non-pharmacological treatment of cognitive impairment in multiple sclerosis primarily involves cognitive rehabilitation. Cognitive rehabilitation interventions are designed to either directly improve cognition or develop strategies to compensate for cognitive impairment (Bobholz, 2003). Results from studies examining the effectiveness of cognitive rehabilitation in persons with MS have been largely disappointing, due to small sample sizes and methodological flaws (Amato, 2006; O'Brien, Chiaravalloti, Goverover, & DeLuca, 2008). This line of research is in its infancy; however, alternative behavioral approaches for managing cognitive dysfunction in persons with MS have been identified, namely, exercise training.

EXERCISE TRAINING AND COGNITION IN MS

Exercise training might represent a behavioral approach for managing cognitive dysfunction in persons with multiple sclerosis, but this area has been understudied. Indeed, there is emerging interest by researchers and clinicians in the effects of fitness (i.e., characteristics of an individual, reflecting aerobic capacity, muscular strength, balance, agility, etc.) and exercise

(i.e., planned behavior aimed towards improving an individual's fitness) on cognition in individuals with MS. To date, two studies have examined cardiorespiratory fitness (a presumed surrogate of aerobic exercise training) as a correlate of cognitive function in MS (Prakash et al., 2007; 2010), and two randomized controlled trials have examined the effects of exercise training on cognition in persons with MS (Oken et al., 2004; Romberg, Virtanen & Ruutiainen, 2005).

Prakash and colleagues (2007) examined cardiorespiratory fitness and cognition, as well as cortical activation patterns in 24 individuals with MS. Cardiorespiratory fitness was assessed using a maximal incremental exercise test on a cycle ergometer in order to measure peak oxygen consumption (VO_2) (Prakash, 2007). Cognition was assessed using a battery of neuropsychological tests, as well as with the PVSAT, a visual administration of the PASAT (Prakash, 2007). Results indicated that greater levels of cardiorespiratory fitness were significantly correlated with faster reaction time on the PVSAT and performance on the PASAT, as part of the neuropsychological battery (Prakash, 2007). Additionally, higher VO_{2peak} scores were associated with greater activation of the right inferior frontal gyrus and middle frontal gyrus (regions of the cerebral cortex), and less activation of the anterior cingulate cortex (Prakash, 2007).

In another study, Prakash and colleagues (2010) examined the relationship between cardiorespiratory fitness, white and grey matter integrity, and cognition in a sample of 21 persons with MS and 15 healthy controls. Cardiorespiratory fitness was represented by peak oxygen consumption during a maximal incremental exercise test performed on a cycle ergometer. Participants also completed a battery of neuropsychological tests including the PASAT, SDMT, and a word generation task. Finally, in order to evaluate white and grey matter integrity, participants underwent an MRI (Prakash, 2010). Higher levels of cardiorespiratory fitness were

associated with better performance on a composite measure of processing speed in persons with MS, as well as with less lesion load volume and greater gray matter volume (Prakash, 2010). This finding suggests that cardiorespiratory fitness, cognition, and white and grey matter integrity are interrelated (Prakash, 2010).

The effects of exercise training on cognition have also been examined in persons with MS. One study employed a 6-month intervention consisting of a weekly yoga class, weekly aerobic exercise class, or wait-list control in 57 individuals with MS (Oken, 2004). Participants were randomized to the yoga, aerobic exercise, or control group. The yoga consisted of a 90 minute session, once per week. The aerobic exercise condition entailed group exercise on a stationary bicycle at the intensity of 2-3 (i.e., minimal exertion) on the Borg RPE scale (Oken, 2004). Sessions took place once per week, and home exercise was encouraged (Oken, 2004). Periodically, participants were given the option of exercising on a Swiss ball rather than cycling (Oken, 2004). Cognition was assessed at both baseline and following the 6th month of the intervention using a battery of neuropsychological tests. Following the completion of the intervention, neither the yoga group nor the exercise group displayed significant improvement in any cognitive measure compared with the wait-list control group (Oken, 2004).

One concern regarding the results of this study is that the aerobic exercise condition took place at an extremely light intensity (e.g., 2-3 on the Borg RPE scale) as well as only once per week, such that the maximal benefits of exercise training on cognition in persons with MS could not be realized. Participation in the weekly classes of either experimental condition was quite low (65%), further curtailing the potentially beneficial effects of aerobic exercise or yoga on cognition in persons with MS. Moreover, the home exercise that was encouraged to participants

was unsupervised, potentially compromising the possible benefits of the aerobic exercise intervention on cognition.

Another study involved 95 persons with MS being randomized into either a 6-month long exercise training intervention or wait-list control group (Romberg, 2005). The exercise training intervention consisted of five resistance training sessions and five aerobic training sessions in the first 3 weeks of the intervention, followed by 23 weeks of a prescribed home exercise regimen (Romberg, 2005). This program, explained by physiotherapists, entailed mainly resistance exercise (e.g., suggested to take place 3-4 times per week) with additional sessions of aerobic exercise (e.g., suggested to take place once per week) (Romberg, 2005). Participants were encouraged via phone to adhere to the home exercise program on four separate occasions over the 6-month intervention (Romberg, 2005). Cognition was assessed at both baseline and after the end of the intervention period with the PASAT. Processing speed did not significantly improve in persons with MS following the exercise intervention (Romberg, 2005).

One concern about the results of this randomized controlled trial is that physical function did not significantly improve in the exercise group over the 6 month period (ES = −0.19), indicating that the exercise prescription was ineffective (Romberg, 2005). Additionally, physical function was assessed through a self-reported measure of quality of life (MSQOL-54), rather than with an objective performance measure. No outcome measures of physical fitness (e.g., muscular strength or aerobic capacity) were taken prior to or following the intervention. A possible factor for the lack of improvement of physical function (and possibly cognition) was the under-regulation of the exercise training program from weeks 4-26 (i.e., only four instances of contact between physiotherapists and participants during a 23-week long intervention).

Such disappointing results from training studies highlight the importance of considering the well-established gerontological literature (Hillman, Erickson & Kramer, 2008) as a way of better informing examinations of fitness, exercise training, and cognition in MS.

FITNESS AND EXERCISE TRAINING ON COGNITION IN OLDER ADULTS

Cognitive impairment too, is common, debilitating, and poorly managed in older adults, and more importantly, there is a wealth of literature indicating that fitness and exercise training are associated with better cognitive performance in this population. Mild cognitive impairment (MCI) is thought to affect nearly 45% of adults over the age of 65 in the United States (Bassuk, Wypij, & Berkman, 2000), and approximately 15% of individuals with MCI will develop dementia (Ritchie, 2004). Dementia has been associated with decreased social functioning, and importantly, mortality (Ritchie, 2004). The prevalence of dementia in the United States is currently estimated at 3.4 million individuals (Plassman et al., 2007).

In general, older adults commonly experience cognitive deficits in domains of attention, executive control, and memory (Hawkins, Kramer, & Capaldi, 1992; Kramer et al., 1999; Grady & Craik, 2000). These decrements can have profound effects on activities of daily life. Cognitive impairment in older adults has been strongly associated with functional decline (i.e., difficulty completing daily tasks including self-care and basic household chores) (Stuck et al., 1999). Further, cognitive impairment has been identified as a major risk factor for increased home care, hospitalization, admission into a nursing home, and mortality (Bassuk, 2000). One longitudinal epidemiological study of community-dwelling older adults (Bassuk et al., 2000) found that both mild and severe cognitive impairment were strongly associated with an increased

risk of mortality. Further, those who experience cognitive decline, independent of the initial extent of cognitive dysfunction, incur an additional risk of mortality (Bassuk, 2000).

There is no FDA-approved pharmacological treatment for cognitive impairment in older adults, and trials of cholinesterase inhibitors (e.g., donepezil) have been disappointing in this population (Gauthier et al., 2006). Non-pharmacological cognitive training interventions specifically designed to target one specific domain of cognition (for example, attempting to improve visual search strategies to enhance executive control) have been successful in laboratory environments, but seem to lack generalizability to everyday situations (Bell et al., 2002).

Fitness and exercise training have been identified as a means to improve cognition in older adults (Kramer, 1999). Early exercise training interventions illustrated that older adults, following participation in an exercise program, demonstrated better performance on cognitive tasks compared to controls (Dustman et al., 1984; Hawkins, 1992). Two major meta-analyses have been published on exercise and cognition in older adults. One meta-analysis reported that exercise training in older adults was associated with overall better performance on cognitive tasks with an average effect size of 0.478 standard deviations (Colcombe & Kramer, 2003). Interestingly, the moderator analysis indicated that combined exercise training (both strength and aerobic training) was associated with greater improvements in cognition than aerobic training alone (Colcombe, 2003). The other meta-analysis reported that exercise training (consisting of a variety of aerobic, strength, and mobility-related exercises) was associated with improved cognitive performance in older adults with documented cognitive impairment, with an average effect size of 0.59 standard deviations (Heyn, Abreu, & Ottenbacher, 2004).

These findings collectively suggest that cardiorespiratory fitness, as well as other domains of fitness (e.g., muscle strength, mobility/balance), have the potential for independent

contributions towards combating cognitive impairment in older adults, and perhaps multiple sclerosis. The gerontology literature provides a backdrop for the proposed study of fitness and cognition in MS by indicating that different types of fitness and modes of training are important when developing interventions to maximize cognitive benefits.

SUMMARY

Multiple sclerosis (MS) is a non-traumatic neurodegenerative disease, characterized by immune-mediated, multi-focal demyelination of white matter in the central nervous system. There is increasing evidence that cognitive impairment is debilitating, highly prevalent, and poorly managed in persons with MS. There are no FDA-approved treatments for cognitive impairment in MS, and trials of pharmacological agents and proposed strategies for cognitive rehabilitation have been conflicting and disappointing. Exercise training has been identified as a possible behavioral approach for managing cognitive dysfunction in MS, largely based on literature of fitness, exercise training, and cognition in older adults. The proposed study will examine relationships among cardiorespiratory fitness, muscle strength, and balance, as components of fitness and cognitive function in persons with MS. This examination of physical fitness will inform the development of subsequent exercise training interventions aimed at improving cognition in persons with MS.

Chapter 3—Methods

PARTICIPANTS

31 ambulatory persons (i.e., ability to walk independently, or with minimal assistance) with a definite diagnosis of MS between the ages of 18 and 54 (males 18-44, and females 18-54), and relapse-free for 30 days, were recruited along with 31 healthy controls (matched by age, height, weight, and gender). All participants lived within a 90 mile radius of Champaign-Urbana, and persons with MS were identified from a pre-existing database consisting of participants from previous studies conducted by our laboratory. Healthy controls were contacted via the provision of public e-mail postings, advertising a study of physical fitness and cognition. Participants were contacted via phone or e-mail and a researcher explained the basic protocol of the study. If the contacted individual was interested in the study, screening and scheduling took place via telephone conversation, during which, each participant was notified of confidentiality procedures, as well as payment information following the completion of the study protocol. Inclusion criteria involved a "no" response on all items of the Physical Activity Readiness Questionnaire (PAR-Q; Thomas, Reading, & Shephard, 1992). If only one "yes" response was given, participants provided a physician's approval in order to engage in the study. More than one "yes" on the PAR-Q resulted in exclusion from the study. A total of 63 persons with MS were contacted with 51 expressing interest in participating. 47 persons were screened, 6 persons did not meet inclusion criteria, and 10 individuals cancelled their testing session (for reasons unrelated to testing), resulting in a subsample of 31 persons with MS. 101 healthy controls were contacted, with 61 expressing interest. Of the 61 who were interested in participation, 32 were matched by age, sex, height, and weight to persons with MS, and one matched control did not meet inclusion criteria, resulting in a final subsample of 31 matched controls.

PRIMARY MEASURES

Fitness

Aerobic Capacity

Aerobic capacity was measured as peak oxygen consumption (VO_{2peak}) using an incremental exercise test on an electronically-braked, computer-driven cycle ergometer (Lode BV, Groningen, The Netherlands) and an open-circuit spirometry system (TrueOne, Parvo Medics, Sandy, UT) for analyzing expired gases. Initially, participants were fitted to the cycle ergometer, and the testing procedures, along with instructions for reporting rating of perceived exertion (RPE) were provided by an investigator. After being fitted with a mouthpiece (Hans Rudolph, Kansas City, MO) for collecting expired gases, the participants performed a 3-minute warm-up at 0 watts. The initial work rate for the exercise test was 0 watts, and the work rate continuously increased at a rate of 15 watts/minute until the participant reached volitional fatigue. With the use of the open-circuit spirometry system, VO_2, respiratory exchange ratio (RER), and work rate were measured continuously and expressed as 20-second averages. Heart rate (HR) was displayed using a Polar heart rate monitor (Polar Electro Oy, Finland), and HR and RPE were recorded each minute during the test. VO_{2peak} was expressed in $ml \cdot kg^{-1} \cdot min^{-1}$ based on highest recorded 20-second VO_2 value when two of three criteria were satisfied: (1) RER $\geq$1.10; (2) peak HR within 10 beats per minute of age-predicted maximum (i.e., ~1 SD); or (3) peak RPE $\geq$17.

Balance

Balance was based upon assessments of the motion of the center of pressure (COP). COP was quantified with a force platform (Kistler model 928/B11, AMTI, Inc.) and data were

collected with a sample frequency of 100 Hz and conditioned with a 4th order Butterworth low pass filter with a cutoff frequency of 5 Hz. Participants stood without shoes on the force platform and maintained a quiet upright stance; use of assistive devices (i.e., cane) was prohibited during the balance protocol. Rather, two spotters were present in order to minimize any risk of falls, and this was consistent over the trial. We sampled a total of two 30 second trials under eyes-open conditions, as per reliability recommendations. Participants were given a short break between each trial. The amount of motion of the COP was indexed by a 95% confidence ellipse, and balance was expressed as the total area (cm^2) of the 95% confidence ellipse of the COP, averaged across both trials.

Muscular Strength

Bilateral isometric knee extensor and flexor peak torque was measured using a Humac Norm Isokinetic dynamometer (CSMI Solutions, Stoughton, MA). Participants were positioned on the dynamometer according to the manufacturer's recommendation. Briefly, the axis of rotation of the machine aligned with the lateral epicondyle of the femur. The calf pad against which the participant exerted force was positioned halfway between the lateral malleolus of the fibula and lateral epicondyle of the femur, and securely attached using straps. A belt was placed over the torso region to minimize movement during the test. We used an anatomical reference position of 90° knee flexion, and isometric torque was assessed at joint angles of 45°, 60°, and 75°, respectively. Peak torque was obtained by having the participant perform 3 maximal contractions with the knee extensors for 5 seconds, which was immediately followed by a 5 second maximal contraction with the knee flexors; 3 sets were performed, per knee. There was not a rest period between contractions within a set, and the rest period between sets was 2 minutes. The highest recorded peak torque for the strongest leg was used as a measure of knee

extensor and flexor isometric strength, and expressed as strength per body weight ($n \cdot m \cdot kg^{-1}$). Our rationale for examining the stronger leg only was that in persons with MS, measuring peak isometric torque in the weaker leg might reflect disease pathology along with physiological de-training, whereas peak torque in the stronger leg would primarily reflect detraining with a lesser disease pathology component.

Cognition

Both the Paced Auditory Serial Addition Test (PASAT) and Symbol Digit Modalities Test (SDMT) were utilized as neuropsychological measures of cognition. The PASAT 3" version is the sole indicator of cognition in the Multiple Sclerosis Functional Composite (MSFC) (Rosti et al., 2007) and is used to assess cognitive processing speed and flexibility. In the 3" version of the PASAT, a series of random single digit numbers are presented at the rate of 1 every 3 seconds via audio recording. Participants are explicitly instructed to orally report the sum of the last two numbers that were presented on the recording. Prior to testing, the experimenter gave an example of how to perform the task correctly, ensuring that the participant understood not to give running totals, but rather, separate sums of the two most recent numbers presented on the tape. Up to three practice trials, consisting of 11 random numbers that were presented at the rate of 1 every 3 seconds, were completed by the participant prior to live testing. During the actual test, an uninterrupted series of 61 random numbers were presented at the same rate. The main outcome measure of the PASAT was the number of correct responses given out of a possible 60.

The written version of the SDMT (Smith, 2010) was used as an assessment of cognitive processing speed. In this task, a series of 9 random geometric symbols are paired with the numbers 1 through 9 in a key. Below the key, a randomized list of 10 symbols with blank boxes

underneath serve as practice items, followed by a similar list of 110 symbols appearing in a random order. Participants were read instructions in order to complete the test correctly, and were instructed to write the number that corresponds to a given symbol in an empty box, according to the way symbols are paired with numbers in the key. Participants completed the 10 practice boxes, while the experimenter ensured the absence of errors. Following the practice trial, participants were given 90 seconds to fill in as many empty boxes as possible, in order, without skipping any. The main outcome measure of the SDMT was the number of correctly written numbers in the 90 second period monitored by the experimenter.

PROTOCOL

For each group (MS or healthy control), the experimental protocol involved two sessions of testing on the University of Illinois at Urbana-Champaign campus, with a week-long period separating each session. The order of assessments during each session was intentionally designed to minimize fatigue. The flow of testing is represented by Figure 1. Prior to any testing, all participants provided written informed consent approved by a University Institutional Review Board. During the first testing session, both neuropsychological assessments were administered, followed by balance testing. Finally, muscle strength was assessed during this session.

All participants began the second testing session by completing a short battery of questionnaires, consisting of a demographics form, and participants with MS further completed the Patient Determined Disease Steps scale (PDDS) (developed as an inexpensive surrogate to the Expanded Disability Status Scale; EDSS; Kurtzke, 1983). Following the completion of questionnaires, all participants underwent an incremental exercise test on a cycle ergometer to

measure peak oxygen consumption. Upon completion of both testing sessions, participants were paid $30.

STATISTICAL ANALYSES

Data were analyzed in PASW Statistics version 18.0 (SPSS Inc., Chicago, IL). We first examined differences between MS and control groups in age, height, and weight using independent-samples *t*-tests. Based on previous work (e.g., Prakash et al., 2007; Prakash et al., 2010) and improved reliability, we next created *z*-scores in PASW for the PASAT and SDMT, and combined the *z*-scores into a composite score for cognitive processing speed (mean of *z*-scores for PASAT and SDMT). Independent samples *t*-tests were then conducted to detect differences between MS and control groups in cognitive performance and fitness. We examined group differences in performance on both the PASAT and SDMT, as well as the composite cognitive processing speed *z*-score, to establish differences in both raw performance and the composite *z*-score. The magnitude of group differences in cognitive and fitness variables between groups was expressed as Cohen's *d* (i.e., difference in mean scores between groups divided by the pooled standard deviation; Cohen, 1985). Values for Cohen's *d* of .2, .5, and .8 were interpreted as small, moderate, and large, respectively (Cohen, 1985). Bivariate correlations were then performed for all measures of fitness and the composite cognitive processing speed variable in the overall sample, and in the MS and healthy control subsamples, separately. Values for correlation coefficients of .1, .3, and .5 were interpreted as small, moderate, and large, respectively (Cohen, 1985). We then performed hierarchical linear regression analysis for examining fitness as a mediator of group differences in cognitive processing speed. This was undertaken by regressing cognitive processing speed on group in Step 1 and then adding fitness

variables that differed between groups and correlated with cognitive processing speed overall in Step 2. We compared the β-coefficient for group between Step 1 and Step 2 to examine if fitness explained group differences in cognitive processing speed. We further compared β-coefficients for the fitness variables for identifying the independent contributions for explaining differences in cognition.

Chapter 4—Results

SAMPLE

Descriptive statistics for the 31 persons with MS and 31 controls are reported in Table 1. There were no statistically significant differences in age ($t = 0.57$, $p = 0.57$), height ($t = -.11$, $p = 0.91$), or weight ($t = 0.95$, $p = 0.35$) between the groups, and the groups had an identical distribution of sex (27 females and 4 males). In the MS subsample, 29 participants (94%) had a relapsing-remitting disease course, and 2 participants (6%) had secondary-progressive MS, and the mean duration of MS was 8.6 (SD=6.3) years. The sample of persons with MS further had minimal disability based on median PDDS scores, and this was expected given the demanding nature of fitness tests.

GROUP DIFFERENCES IN COGNITION AND PHYSICAL FITNESS

The descriptive statistics for the two measures of cognitive performance and three domains of physical fitness for the MS and control subsamples are presented in Table 2. There were statistically significant differences between groups in PASAT performance ($t = -2.137$, $p = .037$) and SDMT performance ($t = -2.690$, $p = .009$). The effect sizes for the PASAT and SDMT were −0.53 and −0.65, respectively, indicating that persons with MS had moderately slowed cognitive processing speed compared with matched controls. There further were significant differences in aerobic capacity ($t = -2.986$, $p = .004$, $d = -0.72$) and balance ($t = 4.126$, $p < .001$, $d = 0.91$) between persons with MS and matched controls. The effect sizes of −0.72 and 0.91 indicated that persons with MS had a moderately reduced VO_2peak and a largely worse balance compared with matched controls, respectively. There were no statistically significant differences between persons with MS and matched controls in knee extensor strength ($t = -0.559$, $p = .578$)

and a nearly significant difference in knee flexor strength ($t = -1.589$, $p = .117$) for the stronger leg, respectively; and this pattern was consistent with results from other studies that reported no differences in knee extensor strength but significant differences in knee flexor strength between persons with MS and healthy controls (Kalron, Achiron, & Dvir, 2011; Chung, Remelius, Van Emmerick, & Kent-Braun, 2008; Lambert, Archer, & Evans, 2001).

CORRELATIONS AMONG PHYSICAL FITNESS AND COGNITION

Correlations among cognitive and physical fitness variables for the overall, MS, and control samples are reported in Table 3. In the overall sample, cognitive processing speed was significantly associated with aerobic capacity ($r = .426$, $p = .001$) and balance ($r = -.516$, $p < .001$), respectively. Cognitive processing speed was not associated with either measure of muscular strength. Within the MS subsample, cognitive processing speed was significantly associated with aerobic capacity ($r = .442$, $p = .013$) and balance ($r = -.520$, $p = .003$) and this is presented using scatter plots in Figure 2. Cognitive processing speed was not associated with either measure of muscular strength in persons with MS. Within the matched control subsample, cognitive processing speed was not significantly associated with aerobic capacity ($r = .310$, $p = .090$), balance ($r = -.038$, $p = .839$), nor either measure of muscular strength.

REGRESSION ANALYSIS

The results for the hierarchical regression analysis are in Table 4. Group (B = .589, SE B = .215, $\beta = .333$) explained a statistically significant ($F(1, 60) = 7.487$, $p = .008$) portion of variance in cognitive processing speed ($R^2 = .111$) in Step 1. In Step 2 of the model, the β for group became attenuated and non-significant ($\beta = .046$, $p = .712$) and aerobic capacity (B = .030,

SE B = .013, β = .273) and balance (B = −.109, SE B = .034, β = −.402) explained a statistically significant (F(3, 58) = 9.898, $p < .001$) amount of variance in cognitive processing speed (R^2 = .339). We did not include muscular strength in the regression analysis since there were no significant group differences in muscular strength, and muscular strength was not associated with cognitive processing speed in the overall, MS, or control samples.

Chapter 5—Discussion

This study examined the relationships among aerobic capacity, balance, and muscular strength with cognitive processing speed in 31 persons with MS and 31 controls matched by age, height, weight, and sex. The primary novel findings were that (a) there were significant differences between persons with MS and controls in aerobic capacity, balance, and cognitive processing speed; (b) in both the overall, and MS subsamples, aerobic capacity and balance were significantly associated with composite processing speed, and these associations were both moderate-to-strong in magnitude; (c) aerobic capacity and balance accounted for differences in cognitive processing speed between persons with MS and controls; and (d) aerobic capacity and balance made significant, independent contributions towards cognitive processing speed.

Such results are important for informing exercise training interventions for improving slowed cognitive processing speed in persons with MS. To date, only two RCTs have examined the effects of exercise training on cognition in persons with MS (Oken et al., 2005; Romberg et al., 2004). Both interventions had methodological concerns (i.e., relied heavily upon unsupervised, home-based exercise; extremely light intensity exercise prescription, such that physical fitness did not improve over the duration of the intervention; self-report measures of physical function, rather than objective measures of fitness) and cognition did not improve following either intervention (Oken et al., 2004; Romberg et al., 2005). Regression analyses from the current investigation identified aerobic capacity and balance as mediators of differences in cognitive processing speed between MS and control groups. Both domains of fitness represent potential targets for improving slowed cognitive processing speed in persons with MS, thus, future exercise training interventions should aim to improve both aerobic capacity and balance as an approach to enhance cognitive processing speed in this population. Importantly, such

interventions in persons with MS should be on par with the scientific rigor of exercise training interventions for improving cognition carried out in older adults (Motl et al., 2011).

Aerobic capacity and balance were both significantly associated with cognitive processing speed in the overall sample, and persons with MS, respectively, and these correlations were of moderate-to-strong magnitude (Cohen, 1985). Further, aerobic capacity and balance made significant, independent contributions for explaining differences in cognitive processing speed between MS and control groups. This is of particular importance as exercise has been proposed to reverse physiological deconditioning (i.e., reductions in aerobic capacity, muscle strength, and balance) in persons with MS (Motl, Goldman, & Benedict, 2010). The current results extend this proposition to include cognitive domains given that aerobic capacity and balance (surrogates of exercise training) were significantly associated with cognitive processing speed, such that increasing physical fitness might mitigate cognitive impairment in persons with MS.

There was not a significant difference in knee extensor strength between groups and there was nearly significant difference between groups in knee flexor strength, and this pattern was consistent with previous findings (Kalron et al., 2011; Chung et al., 2008; Lambert et al., 2001). Additionally, muscular strength was not associated with cognitive processing speed in the overall, MS, or control samples, respectively. Collectively, these data did not support our hypotheses. By extension, knee extensor and flexor strength would seemingly not be ideal targets for improving cognitive processing speed in persons with MS. This was not expected, as a seminal meta-analysis (Colcombe, 2003) reported that combined aerobic and resistance training is associated with improved cognition in older adults (a population who experiences cognitive impairment in domains similar to persons with MS). One potential reason for the lack of an

association between muscular strength and cognitive processing speed in the current study is that muscular power, as opposed to strength, might be associated with faster cognitive processing speed in persons with MS. This is based on several studies that have reported that knee extensor power is associated with better cognition in older adults (Petrella, Miller, & Cress, 2004; Liu-Ambrose, Nagamatsu, Graf, Beattie, Ashe, & Handy, 2010). However, in the current study, both measures of muscular strength were strongly related to aerobic capacity in the overall, MS, and control subsamples, respectively. Further, knee extensor strength was significantly and strongly associated with knee flexor strength in the overall, MS, and control subsamples, respectively. Collectively, these associations are consistent with a large body of literature of muscular strength and aerobic fitness in other populations (e.g., Millet, Jaouen, Borrani, & Candau, 2002). In resistance training studies in persons with MS, isometric leg strength is indeed a commonly reported outcome measure (e.g., White, McCoy, Castellano, Gutierrez, Stevens, Walter, & Vandenborne, 2004; Gutierrez, Chow, Tillman, McCoy, Castellano, & White, 2005; Dalgas et al., 2009), and our protocol was consistent with such methodologies. However, it should be noted that there have been no cross-sectional investigations or RCTs specifically examining muscular strength or muscular power on cognition in persons with MS to establish a gold-standard for outcomes associated with resistance exercise.

One study reported that aerobic capacity was associated with increased white and grey matter integrity and better cognitive processing speed in persons with MS (Prakash et al., 2010). By extension, the associations among aerobic capacity, balance, and cognitive processing speed in persons with MS warrant further exploration into the possible neuroprotective effects of physical fitness, as brain atrophy (e.g., reduced third ventricular width, brain parenchymal volume, etc.) has been predictive of slowed cognitive processing speed in persons with MS

(Benedict et al., 2006). Future exercise training interventions might consider including imaging protocols (i.e., MRI) to assess potential preservation of CNS tissue in response to improved aerobic capacity and balance in persons with MS.

Strengths of the current investigation include the objective measurement of multiple domains of fitness, inclusion of valid neuropsychological measures of cognitive processing speed, and inclusion of controls matched by age, height, weight, and sex. One limitation of the study is the cross-sectional nature of this investigation, as it does not indicate causality between measures of physical fitness and cognitive processing speed. Indeed, cognitive impairment might influence participation in activities aimed to increase physical fitness, as much as physical fitness influences cognitive processing speed. Our sample was primarily female (87%), with a disproportionately larger ratio of females than males compared with the overall gender bias of the disease (i.e., females are 2-3 times more likely than males to have MS; Noonan et al., 2010). Finally, this study was advertised as an examination of physical fitness and cognition to both persons with MS and controls, and there might have been an upward bias of participation in exercise behavior in the overall combined sample. However, *post-hoc* independent samples *t*-tests indicated that there was not a significant difference in self-reported exercise sessions per week ($t = -1.133$, $p = .131$) between persons with MS and matched controls.

Chapter 6—Conclusions

Cognitive impairment, particularly slowed cognitive processing speed, is prevalent, disabling, and poorly-managed in persons with MS. Overall, there were significant differences in aerobic capacity, balance, and cognition between persons with MS and controls matched by age, sex, height, and weight. Aerobic capacity and balance were significantly associated with cognitive processing speed in persons with MS, and these associations were both moderate-to-strong in magnitude. Further, aerobic capacity and balance accounted for differences in cognitive processing speed between persons with MS and controls and made significant, independent contributions for explaining such differences in cognitive processing speed. Such results are important for informing future exercise training interventions such that enhancing aerobic capacity and balance, but not muscular strength, represent targets for improving slowed cognitive processing speed in persons with MS.

Chapter 7—Tables and Figures

Figure 1: Flow of Testing

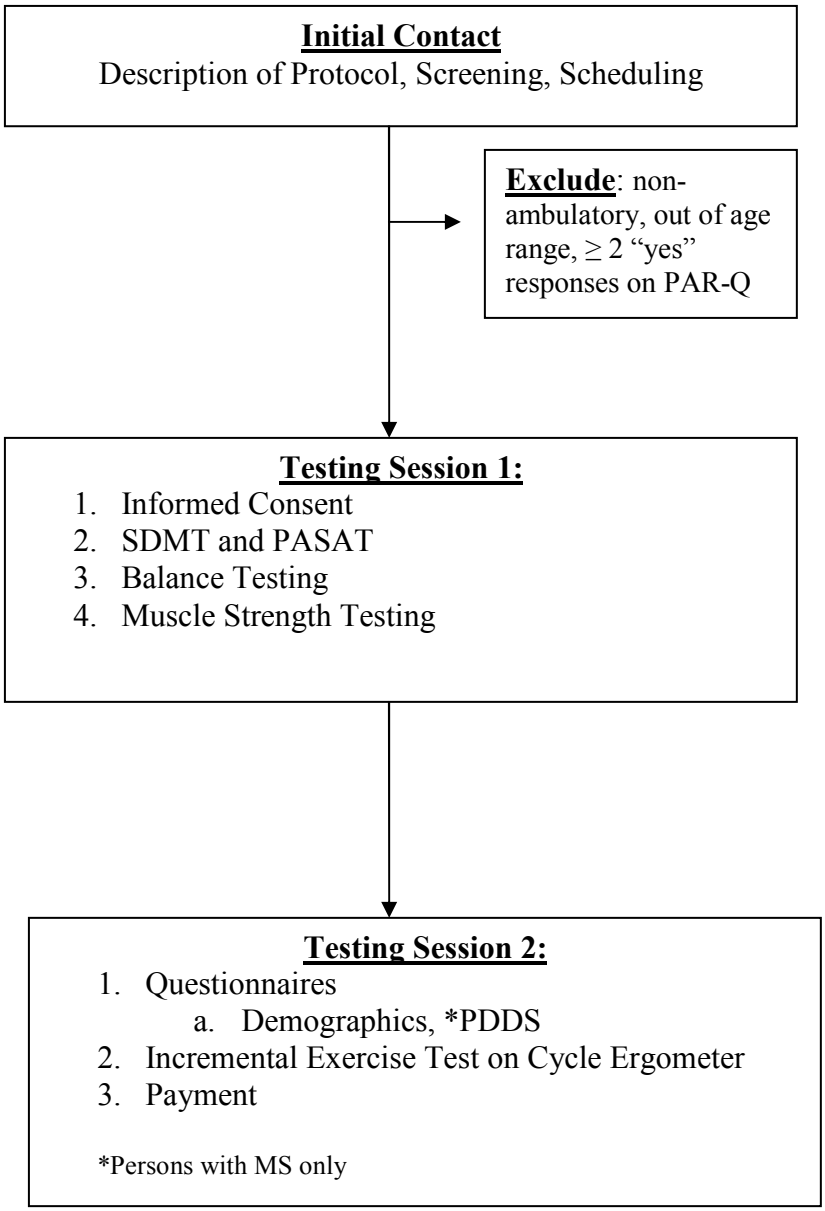


Table 1: Demographic Characteristics of 31 persons with MS and 31 healthy controls matched by age, sex, height, and weight.

Variable	MS (n=31)	Controls (n=31)
Age (years)	43.4 (7.7)	42.4 (7.5)
Sex (n,% female)	27/31, 87.1%	27/31, 87.1%
Height (cm)	170.8 (8.7)	171.0 (8.6)
Weight (kg)	75.2 (16.4)	71.5 (13.5)
MS Type (n, % RRMS)	29/31, 93.5%	-
MS Duration (years)	8.6 (6.3)	-
PDDS Score (median, range)	2 (0-5)	-

Note: Data are presented as mean (*SD)* unless noted otherwise; RRMS=Relapsing-remitting multiple sclerosis; PDDS=Patient-determined disease steps

Table 2: Cognitive performance and physical fitness data for 31 persons with MS and 31 healthy controls matched by age, sex, height, and weight

Variable	MS (n=31)	Controls (n=31)
PASAT Performance	44.6 (12.2)	49.9 (6.5)
SDMT Performance	51.7 (13.5)	59.5 (8.9)
VO_2peak (ml/kg/min)	23.5 (6.4)	29.3 (8.8)
95% COP Ellipse (cm^2)	5.2 (3.9)	2.2 (1.5)
Maximal Knee Extensor Strength (Strong) (n·m/kg)	2.1 (0.5)	2.2 (0.5)
Maximal Knee Flexor Strength (Strong) (n·m/kg)	0.5 (0.2)	0.6 (0.2)

Note: Data are presented as mean (*SD)*; PASAT=Paced Serial Auditory Addition Test; SDMT=Symbol Digit Modalities Test; COP=Center of Pressure;

Table 3a: Correlations among variables for the overall sample of 31 persons with MS and 31 healthy controls matched by age, sex, height, and weight

Overall Sample (n=62)

Variable	1.	2.	3.	4.	5.
1. CPS	-				
2. VO_2peak	.43*	-			
3. 95% COP Ellipse	-.52*	-.34*	-		
4. Maximal KE Strength (Strong)	.14	.56*	-.19	-	
5. Maximal KF Strength (Strong)	.22	.70*	-.20	.64*	-

Note: * $p<.05$ with 2-tailed test; CPS=Cognitive Processing Speed; COP=Center of Pressure; KE=Knee Extensor; KF=Knee Flexor

Table 3b: Correlations among variables for 31 persons with MS

MS (n=31)

Variable	1.	2.	3.	4.	5.
1. CPS	-				
2. VO_2peak	.44*	-			
3. 95% COP Ellipse	-.52*	-.38*	-		
4. Maximal KE Strength (Strong)	.03	.58*	-.23	-	
5. Maximal KF Strength (Strong)	.13	.52*	-.19	.62*	-

Note: * $p<.05$ with 2-tailed test; CPS=Cognitive Processing Speed; COP=Center of Pressure; KE=Knee Extensor; KF=Knee Flexor

Table 3c: Correlations among variables for 31 healthy controls matched by age, sex, height, and weight

Controls (n=31)

Variable	1.	2.	3.	4.	5.
1. CPS	-				
2. VO_2peak	.31	-			
3. 95% COP Ellipse	-.04	-.01	-		
4. Maximal KE Strength (Strong)	.31	.58*	-.11	-	
5. Maximal KF Strength (Strong)	.25	.79*	-.02	.65*	-

Note: * $p<.05$ with 2-tailed test; CPS=Cognitive Processing Speed; COP=Center of Pressure; KE=Knee Extensor; KF=Knee Flexor

Table 4: Summary of hierarchical regression analysis for predicting cognitive processing speed in persons with MS (n=31) and controls (n=31)

Variable	*B*	*SE B*	*β*
Step 1			
Group	0.59	0.22	0.33*
Step 2			
Group	0.08	0.22	0.05
VO_2peak	0.03	0.01	0.27*
Balance	−0.11	0.03	−0.40*

Note: R^2=.11 for Step 1; ΔR^2=.23 for Step 2 (p<.05, two-tailed test). *p<.05 with one-tailed test.

Figure 2a: Scatter plot of composite cognitive processing speed (CPS) performance and VO2peak in 31 persons with MS, along with line of best fit and 95% confidence interval.

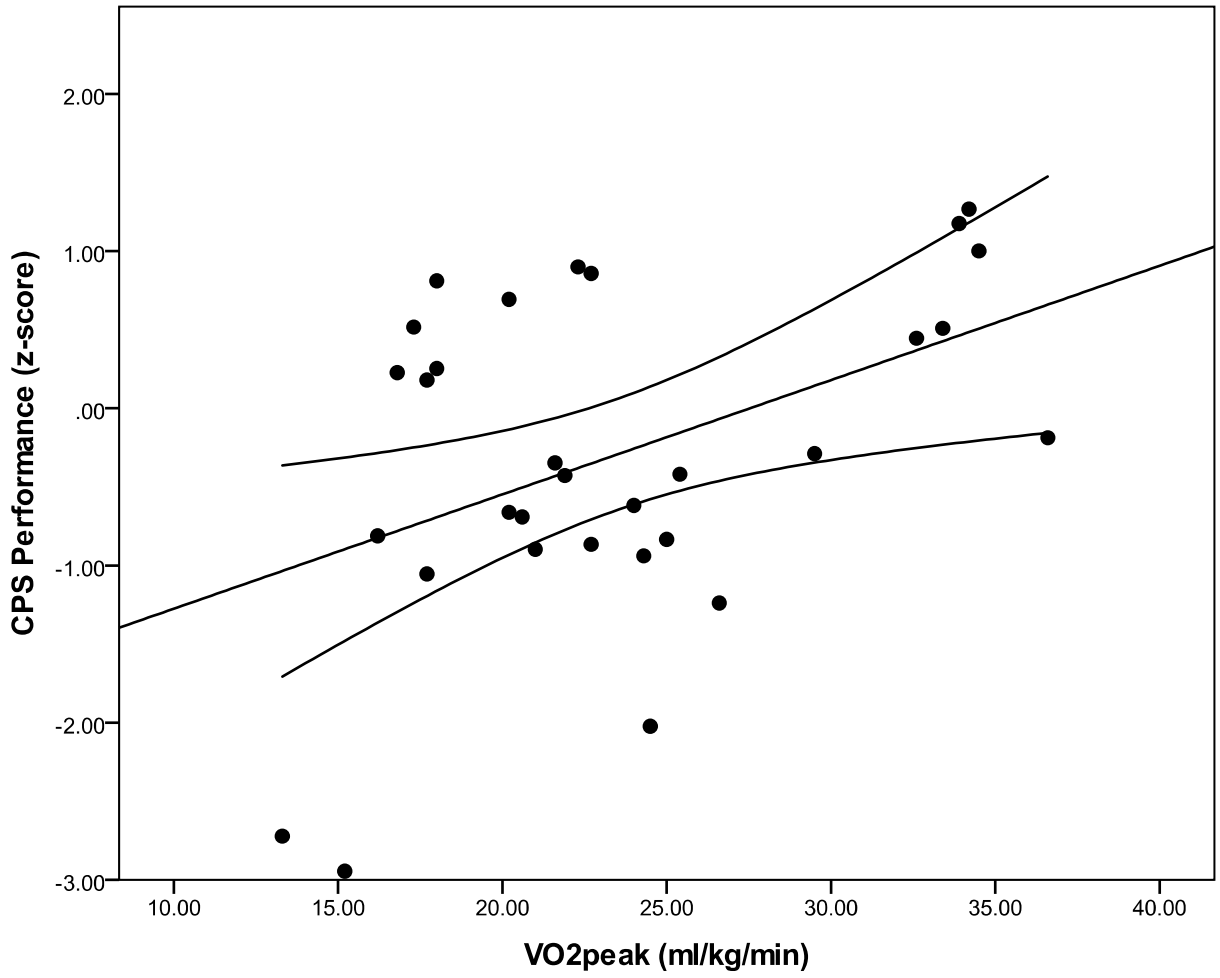
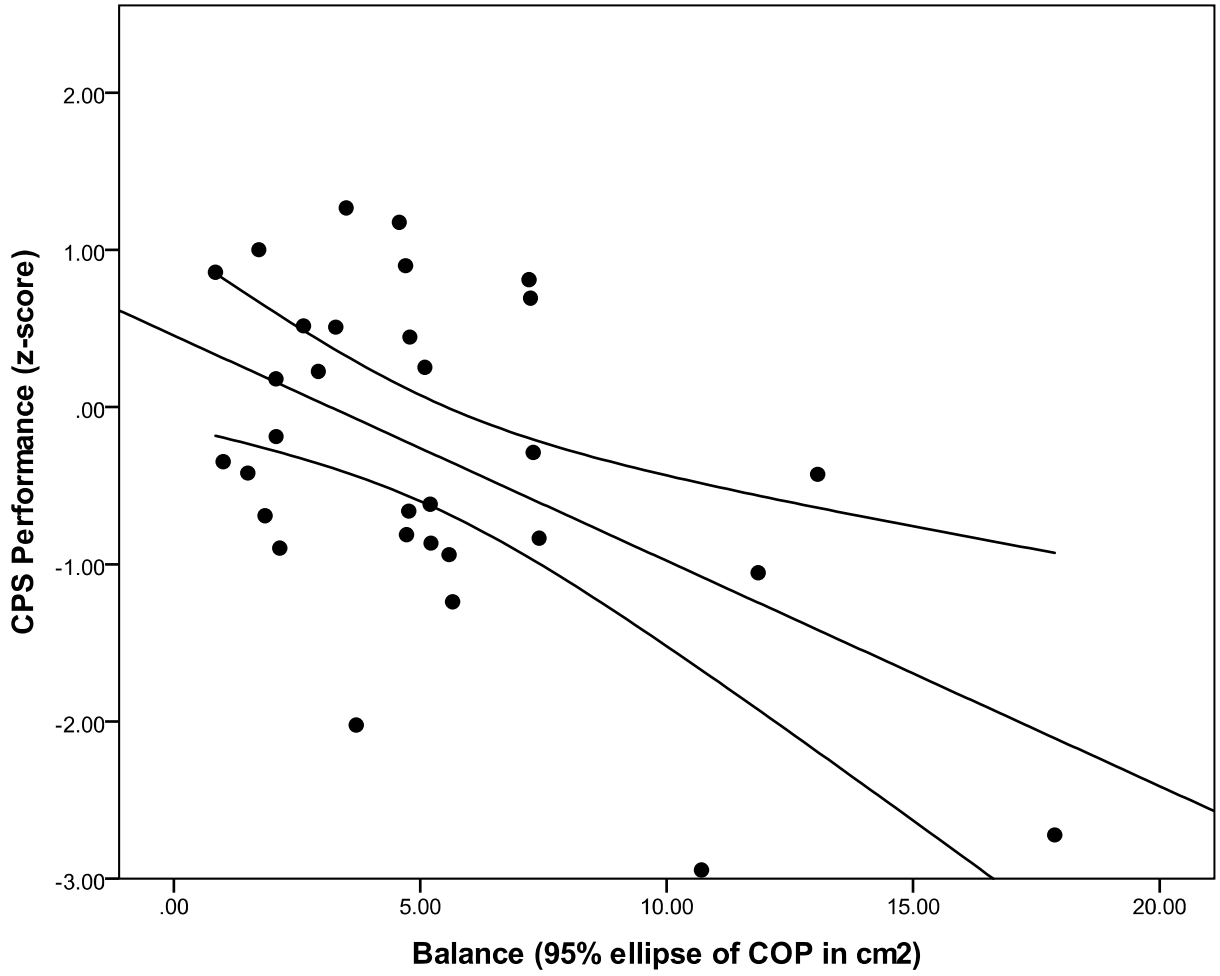


Figure 2b: Scatter plot of composite cognitive processing speed (CPS) performance and balance in 31 persons with MS, along with line of best fit and 95% confidence interval.



Note: COP=Center of Pressure

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