THE ACUTE EFFECTS OF VARYING INTENSITIES OF TREADMILL WALKING EXERCISE ON COGNITION IN PERSONS WITH MULTIPLE SCLEROSIS

BY

BRIAN SANDROFF

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, 2015

Urbana, Illinois

Doctoral Committee:

Professor Robert W. Motl, Chair, Director of Research
Professor Charles H. Hillman
Professor Edward McAuley
Assistant Professor Lara A. Pilutti
Professor Ralph H.B. Benedict, University at Buffalo, State University of New York

Abstract

Background: Exercise training represents a promising approach for managing cognitive impairment in persons with multiple sclerosis (MS). There is preliminary evidence that treadmill walking exercise might be the modality of exercise that exerts the greatest beneficial effects on executive control in persons with mild MS disability. However, the dose-dependent effects of varying intensities of treadmill walking exercise on this cognitive function are unknown. Such an investigation is critical for providing the final data for delineating the optimal exercise stimulus (or stimuli) for improving executive control in persons with MS.

Objectives: The present study compared the acute effects of light, moderate, and vigorous intensity treadmill walking exercise on multiple aspects of executive control (i.e., interference control and response inhibition) relative to quiet rest in 24 persons with mild MS disability, using a within-subjects, repeated-measures experimental design.

Methods: Participants completed four experimental conditions that consisted of 20 minutes of light intensity treadmill walking exercise, moderate intensity treadmill walking exercise, vigorous intensity treadmill walking exercise, and quiet rest in a randomized, counterbalanced order. Participants underwent a modified-flanker task and Go/No-Go task as measures of executive control immediately prior to and following each condition.

Results: Repeated-measures ANOVAs indicated large, statistically significant pre-to-post reductions in the cost of interfering stimuli on reaction time, but not accuracy, on the modified-flanker task for light, moderate, and vigorous intensity exercise compared with quiet rest

(F(3,69)=4.27,p=.01,η_p^2=.16) that were similar in magnitude. There further were no overall effects of exercise intensities on percent accuracy from the Go/No-Go task (F(3,69)=0.33,p=.81,η_p^2=.01), compared with quiet rest.

Conclusions: The present results support light, moderate, and vigorous intensity treadmill walking as exercise stimuli that might particularly benefit speed-related aspects of executive control (i.e., interference control of reaction time). This represents the final step in delineating the optimal exercise stimuli for inclusion in a subsequent longitudinal exercise training intervention for improving this cognitive function in persons with mild MS disability.

Acknowledgments

First and foremost, I would like to thank my advisor, Professor Rob Motl, for everything over the past six years of my graduate study in the Exercise Neuroscience Research Laboratory, and the year before that as a goofy undergraduate research assistant looking for some career advice. Without question, Rob has been the absolute ideal mentor and a constant inspiration. Rob leads by example, and has been a central role model for how to be an excellent scholar, scientist, and overall good person. After working with him for the past seven years, I have full confidence that I will succeed going forward, because I have been trained by the best. I have learned so much over my time in the lab and have had countless great conversations with Rob over the years that I will always value. No matter where my future research agenda takes me, I look forward to staying in close contact with Rob as my career matures. To Rob—Machu Picchu.

I would also like to thank my committee of Professors Ralph Benedict, Chuck Hillman, Eddie McAuley, and Lara Pilutti. Your guidance throughout the dissertation process has undoubtedly made this study more methodologically sound. Thank you for going the extra mile in helping me to become a better, stronger research scientist. On a personal note, I always enjoy interacting with each of you, whether it's in a formal lecture setting or an informal conversation. I am incredibly lucky that I have four other mentors who are always willing to lend an ear and enthusiastically provide helpful feedback. Additional thanks in advance to my future mentor, Dr. John DeLuca, for helping me successfully transition to a fully independent scientist, using my background and training as a springboard.

Of course, I would like to acknowledge the cast of characters in the ENRL who have made this journey so enjoyable: (in order of appearance) Elise, Yoojin, Madeline, Dee, Swathi, Lara (again), Rachel, Shauna, Ipek, Yvonne, Julia, Lizzie, Dom, Sarah, and Brynn. I greatly

appreciate all the times you went out of your way to lend a hand, had random brainstorming sessions, provided helpful comments on papers, had a laugh, listened, and/or ran research projects with me at some point during my time in the lab. Hopefully we'll stay in touch over the years, and although I may be leaving the lab, I'm just an e-mail away. But please don't ask me to help fix the K4b2—do it yourself! Humor aside, thanks as well to the many undergraduate research assistants in the ENRL who have aided in the research process. Additionally, none of my work would be possible without the research participants themselves. Thank you so very much for generously volunteering your time and giving back to help others with multiple sclerosis—truly inspiring.

Finally, I would like to thank my friends and family for all the love and support over the years, especially Mom, Dad, Michelle, and Tiffani (and Max too). Although I want to acknowledge this amazing support structure, and how grateful I am for everything they've inspired me to do in this process, I'm truly excited about what the future holds for us in this upcoming adventure!

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Chapter 1—Introduction

Multiple sclerosis (MS) can be described as a non-traumatic, immune-mediated and neurodegenerative disease of the central nervous system (CNS) with an estimated prevalence of 1 per 1000 people in the United States (e.g., Wallin et al., 2000). This disease is initially characterized by multi-focal areas of inflammation resulting in demyelination in the CNS (Trapp & Nave, 2008). The disease process eventually causes irreversible damage (i.e., neurodegeneration) of both grey and white matter in the brain, resulting in the accumulation of both physical and cognitive disability.

Cognitive impairment is highly prevalent in MS, with upwards of 50% of patients demonstrating cognitive impairment based on performance on neuropsychological tests (Chiaravalloti & DeLuca, 2008; Benedict & Zivadinov, 2011). Such cognitive impairment primarily manifests as slowed cognitive processing speed, impaired learning and memory, and executive dysfunction, but less so as impairment in intellectual functions and language skills (Benedict & Zivadinov, 2011; Prakash et al., 2008). For example, one recent meta-analysis reported moderate-sized effects of relapsing-remitting MS (RRMS) on overall cognitive function ($g = -0.59$), as well as on the cognitive domains of attention and executive function ($g = -0.56$); there were smaller effects of RRMS on verbal functions and language deficits ($g = -0.44$) (Prakash et al., 2008). There further is meta-analytic evidence that suggests that processing speed, learning and memory, and executive function are even more impaired in persons with chronic progressive presentations of MS compared with relapsing-remitting presentations of the disease (Zakzanis, 2000).

Cognitive impairment is a highly disabling consequence of MS and has been associated with many negative health outcomes. For example, slowed cognitive processing speed and

executive dysfunction have been associated with depression in MS (Bobholz & Rao, 2003; Arnett et al., 2001), although this relationship is not fully understood (e.g., Arnett, Barwick, & Beeney, 2008). Cognitive impairment and decline have further been associated with unemployment and loss of employment, respectively, in persons with MS (Morrow et al., 2010; Benedict et al., 2005), as well as the loss of driving abilities (Shawaryn et al., 2002; Lincoln & Radford, 2008). There is additional, longitudinal evidence that decreased performance on a battery of neuropsychological tests is associated with loss of independence, increased need for substantial assistance with activities of daily living (i.e., greater than 3 hours per day), and social isolation over time in persons with MS (Amato et al., 2001).

Cognitive impairment is poorly managed in persons with MS. There is limited support for disease-modifying treatments (e.g., interferon-beta-1a) for mitigating cognitive impairment, and this is largely based on methodological concerns in several randomized controlled trials (RCTs; Amato et al., 2013). For example, one three-year study of patients with RRMS with mild disability reported that high doses of interferon-beta-1a were associated with a 32% reduction in risk for cognitive decline, based on neuropsychological test performance (Patti et al., 2010). However, an untreated control group or placebo condition was not included in the study to directly determine to what extent interferon-beta-1a prevented cognitive decline, thus the results from that study should be interpreted with caution (Patti et al., 2010). There further is equivocal evidence for the efficacy of symptomatic pharmacological treatments for MS-related cognitive impairment in general, and there are no US Food and Drug Administration (FDA)-approved symptomatic treatments specifically for slowed cognitive processing speed and executive dysfunction in this population.

There is conflicting evidence for the efficacy of cognitive rehabilitation interventions on slowed cognitive processing speed and executive dysfunction in this population (Amato et al., 2013). One review highlighted the complete lack of cognitive rehabilitation interventions directly targeting slowed cognitive processing speed in MS (Amato et al., 2013). In addition, this review outlined the lack of convincing evidence for specific cognitive rehabilitation interventions for executive dysfunction in MS, though there is weak evidence that generalized cognitive training might improve executive functioning (Amato et al., 2013). This underscores the importance of considering alternative approaches for managing cognitive impairment in persons with MS. One such approach involves exercise training (Motl, Sandroff, & Benedict, 2011).

There have been three published RCTs of exercise training on cognition in persons with MS. The first two RCTs involved the effects of largely unsupervised yoga and aerobic exercise or combined aerobic and resistance exercise, respectively (Oken et al., 2004; Romberg et al., 2005), and reported no significant intervention effects on physical fitness or cognitive function in persons with mild MS disability. By definition, exercise is a planned, structured, repetitive physical activity behavior with the goal of increasing physical fitness (Bouchard & Shephard, 1994). Demonstrating an improvement in physical fitness is a key manipulation check for gauging the success of any exercise training intervention (Motl, Pilutti, & Sandroff, 2013).

The other RCT examined the effects of a supervised, aerobic exercise training intervention on fitness and cognitive function in persons with progressive MS (i.e., moderate disability). Those who underwent cycle ergometer training demonstrated significant improvements in cardiorespiratory fitness and improvements in verbal memory and alertness, but not in cognitive processing speed or executive function, compared with a wait-list control group (Briken et al., 2014). The lack of an improvement in cognitive processing speed and executive

function from the latter RCT is partially consistent with a growing pattern of results from studies that suggests that physical fitness and physical activity, respectively, are associated with cognitive processing speed in persons with mild, but not moderate, MS disability (Sandroff, Pilutti, Benedict, & Motl, 2015b; Sandroff, Pilutti, Dlugonski, & Motl, 2013; Sandroff, Klaren, Pilutti, Dlugonski, Benedict, & Motl, 2014); those effects on executive functioning have not been studied. Importantly, the equivocal results from the RCTs highlight the importance of considering the well-established body of literature in the general population that documents robust, beneficial effects of exercise training on executive functioning across the lifespan (i.e., healthy children, young adults and older adults) (Hillman, Erickson, & Kramer, 2008). This approach serves as a way of better informing exercise training interventions on cognition in mild MS. The equivocal RCT results in MS further warrant examination of preliminary evidence of exercise effects on cognition in other *neurological* populations (McDonnell, Smith, & Mackintosh, 2011) to provide support for the feasibility of such a trial in MS.

The effects of exercise training on cognition in the general population, across the lifespan, have been summarized by meta-analyses on this association in healthy children, younger adults, and older adults, respectively. One meta-analysis reported that physical activity was associated with improved cognitive performance in children with an overall effect size of 0.32 standard deviations (Sibley & Etnier, 2003). Following this meta-analysis, several well-designed RCTs have reported that exercise training has been associated with improvements in executive control among children. For example, one recent RCT reported that following a 9-month exercise intervention, 8 and 9-year old children demonstrated improvements in one aspect of executive control based on response accuracy on task conditions requiring the upregulation of inhibitory control relative to children randomized to a wait-list control condition (Chaddock-

Heyman et al., 2013). Another noteworthy result from this study was that at follow-up, children who participated in the intervention demonstrated accuracy rates similar to those of young adults (Chaddock-Heyman et al., 2013). Exercise is associated with cognitive function in healthy adults, and this is further based on meta-analytic evidence (Smith et al., 2010). One such meta-analysis reported that aerobic exercise was associated with improved attention/processing speed (g = 0.16) and executive function (g = 0.12) in adults over 18 years old (Smith et al., 2010). Age did not moderate those associations, which suggests that the beneficial effects of exercise on cognition were relatively equal across the span of adulthood (Smith et al., 2010). There is a large body of evidence that suggests that exercise is associated with cognitive function in older adults. One seminal meta-analysis reported that exercise training was associated with overall better performance on cognitive tasks in older adults with an average effect size of 0.48 standard deviations (Colcombe & Kramer, 2003). This meta-analysis indicated that there is a selective benefit of exercise training, such that the largest beneficial effects of exercise occur for executive control processes (g = 0.68; Colcombe & Kramer, 2003). There further is preliminary evidence that exercise training is associated with improvements in cognitive functioning in persons with neurological disorders (i.e., schizophrenia, stroke, traumatic brain injury (TBI); McDonnell et al., 2011), though the number of RCTs in those populations is substantially smaller than in healthy children, younger adults, and older adults.

The delineation of exercise stimuli for such successful interventions across the lifespan in the general population (and to a lesser extent in persons with neurological disorders) is, in part, based on examinations of the effects of acute bouts of aerobic exercise on cognitive function (Tomporowski, 2003; Lambourne & Tomporowski, 2010; Chang, Labban, Gapin, & Etnier, 2012). An important assumption is that the acute effects of single bouts of exercise on cognition

will be additive and cumulative, much like adaptations on cardiorespiratory fitness (Haskell, 1994), during longitudinal exercise training interventions. This increases the potential for the realization of meaningful improvements in cognition. The overall effects of acute exercise on cognitive functioning have been summarized by two recent meta-analyses (Lambourne & Tomporowski, 2010; Chang et al., 2012). The most recent meta-analysis reported overall modest effects of acute aerobic exercise on cognitive function (Cohen's d = 0.10). Moderator analyses revealed larger effects for tests of executive function when administered either immediately following exercise (d = .19) or after a delay period following exercise (d = .17) (Chang et al., 2012). Those effects were applicable across the lifespan, such that acute exercise was significantly associated with cognition in children (d = .17), younger adults (d = .07), middle-aged adults (d = .18), and older adults (d = .18) (Chang et al., 2012). To that end, we recently completed a pilot study that identified a large, statistically significant pre-to-post reduction in the cost of interfering stimuli on reaction time (i.e., interference control of reaction time; RT) on a modified flanker task for an acute bout of treadmill walking exercise relative to a quiet rest control condition (η_p^2 = .17) in 24 persons with mild MS disability (Sandroff, Hillman, Benedict, & Motl, 2015a). There were no statistically significant pre-to-post reductions in interference control of RT on the modified flanker task for cycle ergometry or yoga relative to quiet rest; there further were no effects identified for any of the conditions for cognitive processing speed, based on Symbol Digit Modalities Test (SDMT) scores, perhaps due to carry-over effects (Sandroff et al., 2015a).

The results from that pilot study suggest that treadmill walking is the modality of exercise that might exert the largest beneficial effects of exercise on executive control in persons with mild MS disability. However, prior to developing a RCT on the effects of chronic treadmill

walking exercise on executive control in mild MS, it is necessary to examine the dose-dependent effects of varying intensities of treadmill walking exercise on executive control in this population. Such an endeavor would then identify the optimal exercise stimulus (i.e., modality and intensity) for inclusion in a well-designed clinical trial of exercise training and cognition in mild MS. This would maximize the potential for persons with MS to demonstrate meaningful improvements in executive control, as presumably, the acute effects of treadmill walking exercise on executive control will be additive and cumulative when the optimal intensity of treadmill walking exercise is included as the primary stimulus in a longitudinal training study.

The current study involved the examination of the effects of twenty-minute bouts of light, moderate, and vigorous intensity treadmill walking exercise compared with a quiet rest control condition on executive control in persons with MS. Based on previous research using modified flanker and Go/No-Go paradigms in healthy control subjects (Pontifex, Saliba, Raine, Picchhietti, & Hillman, 2013; Gothe, Pontifex, Hillman, & McAuley, 2013; Kamijo et al., 2004; Drollette, Shishido, Pontifex, & Hillman, 2012), the primary hypothesis was that walking at a moderate intensity would exert the strongest acute effects on executive control compared with light and vigorous intensity walking, respectively, relative to quiet rest. The secondary hypothesis was that those effects would be larger in cognitive tasks requiring greater levels of executive control. If successful, this line of research will ultimately provide clinicians and patients with better guidelines for using chronic exercise training as an approach for the management of cognitive impairment as a highly prevalent, poorly-managed, and life-altering symptom of MS.

Chapter 2—Review of Literature

OVERVIEW

The current review of literature provides critical information for developing the rationale for the design of the present study of the acute effects of varying intensities of treadmill walking exercise on cognition in persons with MS. This chapter first describes the epidemiology of MS (i.e., incidence, prevalence, genetic/environmental risk factors), followed by a brief section on the clinical course of the disease along with the pathophysiological mechanisms that manifest as physical and cognitive disability. This chapter then discusses the highly-prevalent and disabling nature of cognitive dysfunction in MS as well as the body of equivocal evidence for pharmacological and non-pharmacological approaches for managing cognitive dysfunction in this population. Based on the conflicting evidence for those approaches, this chapter then reviews research examining exercise training as an alternative approach for managing this prevalent and disabling feature of MS. As the research on exercise and cognition in MS is in its infancy, the current chapter discusses results from studies of the effects of chronic exercise training and acute bouts of exercise, respectively, on cognitive functioning in other populations. This serves as a backdrop for better informing studies of exercise and cognition in MS. This chapter then concludes with a brief summary of the rationale and experimental design of the current study, within the context of the previously described research in persons with MS and other populations.

EPIDEMIOLOGY OF MS

MS can be described as a non-traumatic, immune-mediated and neurodegenerative disease of the CNS that typically presents in the 3rd or 4th decade of life (Wallin, Page, &

Kurtzke, 2000; Mayr, Pittock, McClelland, Jorgensen, Noseworthy, & Rodriguez, 2003). As of the year 2000, median age of diagnosis was reported to be 37.2 years (Mayr et al., 2003), and median survival has been reported to be between 30-43 years following diagnosis (Wallin et al., 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 et al., 2003).

MS is among the most common neurological diseases worldwide, with a global prevalence thought to exceed 2 million cases (Kingwell et al., 2013). Based on a systematic review of epidemiological studies across the globe (Koch-Henriksen & Sorenson, 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 & Sorenson, 2010). Accordingly, MS is more common in individuals with Northern European ancestry than those of Hispanic, African, or Asian descent (Williamson, Henry, Schiffer, & Wagner, 2007; Mayr et al., 2003). In the United States, MS has an estimated prevalence of 1 per 1000 people (Wallin et al., 2000; Mayr et al., 2003; Koch-Henriksen & Sorenson, 2010; Williamson et al., 2007; Noonan, Kathman, & White, 2002). Within the United States, geographically, MS is most prevalent in the northern states and less so in southern states (Wallin et al., 2000; Williamson et al., 2007).

To date, a singular cause of MS has not been identified, though there is support for both genetic and environmental risk factors. Despite MS not being typified as a genetic disorder with a single major locus (e.g., Huntington's Disease), there is evidence to suggest a maternal parent-

of-origin effect in MS, and that MS is linked with HLA genes (Ramagopalan, Dobson, Meier, & Givoannoni, 2010). Epidemiological data further support environmental risk factors for MS. To that end, one recent review highlighted Epstein-Barr virus (EBV) infection, smoking, and Vitamin D deficiency as contributing risk factors for the disease (Ramagopalan et al., 2010). Infection with EBV and subsequent diagnosis of mononucleosis is associated with an increased risk of MS. Studies have reported that approximately 99% of persons with MS have previously been infected with EBV (e.g., Ascherio & Munger, 2007), whereas 94% of healthy controls have previously been infected (Ramagopalan et al., 2010). This suggests that EBV infection is not specific to MS, although there further seems to be an increased risk of MS if infected with EBV during adulthood compared with childhood EBV infection (Ascherio & Munger, 2007).

Smoking has also been identified as a risk factor for MS. One meta-analysis reported a 1.51 pooled odds ratio of MS diagnosis for smokers versus non-smokers (Hawkes, 2007); there further seems to be a dose-response effect among smokers such that a greater volume of smoking (e.g., smoking more cigarettes) is associated with a substantially larger risk for MS (Hawkes, 2007). Although EBV infection and smoking represent potential environmental risk factors, there is a considerably larger body of literature examining Vitamin D deficiency as a risk factor for MS.

Globally, there is a trend for increased prevalence of MS in temperate climates, particularly with increasing latitude (i.e., increasing distance from the Equator) (Koch-Henriksen & Sorenson., 2010; Ramagopalan et al., 2010), where there is a general lack of sunlight exposure. Reviews and meta-analyses have identified Vitamin D as a potential mediator of the association between latitude/sunlight exposure and MS prevalence (Ascherio, Munger, & Simon, 2010; Ramagoplan et al., 2010), and have further identified Vitamin D to have an independent,

protective effect against MS (Ascherio et al., 2010). However, one limitation to the Vitamin D hypothesis is that the proposed mechanisms of its protective effect against MS are not well-understood.

CLINICAL DISEASE COURSE AND UNDERLYING PATHOPHYSIOLOGY OF MS

MS was first recognized and popularized as a progressive neurologic disease involving multiple lesions of variable size and distribution throughout the CNS by Charcot in 1868 (Hickey, 1999). Over the past 147 years, there have been many descriptions of the clinical course and underlying pathophysiological mechanisms of MS that have been continually revised and refined with advancements in technology and research methodology. The current section presents a brief review of the presently accepted views on the clinical course and pathophysiological mechanisms of MS.

Prior to a definite diagnosis of MS, a majority of patients experience clinically isolated syndrome (CIS) (Miller, Chard, & Ciccarelli, 2012). CIS is defined as the first clinical episode in which a patient demonstrates signs and symptoms that might be suggestive of an inflammatory, demyelinating CNS disease (e.g., MS). Approximately 30-70% of CIS cases result in an eventual MS diagnosis (Miller et al., 2012). There are relapsing and progressive presentations of MS. Approximately 85% of patients experience a clinical 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 & Nave, 2008; Smith & McDonald, 1999; Vollmer, 2007; Mitchell, Benito-Leon, Morales Gonzales, Rivera-Navarro, 2005). These relapses are attributed to instances of acute inflammation (i.e., acute demyelinating lesions) in the CNS, which cause damage to myelinated

axons and neurons (Vollmer, 2007), subsequently hindering neuronal conduction. There is not a 1:1 ratio of lesions to relapses; rather, the number of demyelinating brain lesions seems to outnumber the number of relapses 10:1, which suggests that that MS might have underlying pathology that is clinically silent (Trapp & Nave, 2008). Although axonal loss is highly prevalent in acute inflammatory demyelinating MS lesions, acute lesions are not strongly associated with permanent disability.

In the period following this acute inflammation (i.e., remission phase), growth factors promote remyelination of damaged axons in the CNS (Vollmer, 2007; Smith & McDonald, 1999). Those 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, without relapses, termed secondary progressive MS (SPMS) (Trapp & Nave, 2008; Smith & McDonald, 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 & Nave, 2008; Smith & McDonald, 1999). PPMS is generally later onset than RRMS, and both progressive disease courses have been linked to axonal degeneration (Trapp & Nave, 2008; Smith & McDonald, 1999).

Axonal degradation, which is initially triggered by chronic demyelination associated with progressive MS, leads to irreversible neurological disability (Confavreux & Vukusic, 2006; 2014; Vollmer, 2007; Trapp & Nave, 2008; Smith & McDonald, 1999). During progressive presentations of MS, the CNS can no longer compensate for additional neuronal loss, such that

brain atrophy occurs in the absence of new inflammatory demyelinating lesions. This suggests that mechanisms other than inflammatory demyelination are responsible for irreversible neurologic impairment (Trapp & Nave, 2008; Confavreux & Vukusic, 2006; 2014). 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 & Nave, 2008). The other proposed mechanism for this degenerative process is that following chronic demyelination, axons degenerate due to increases in intracellular calcium (Ca^{2+}), which eventually leads to axonal loss (Trapp & Nave, 2008).

A key issue regarding the underlying pathophysiological mechanisms involves the shift from immune-mediated, inflammatory disease processes to largely neurodegenerative disease processes. As such, a major goal of treatment is to prevent relapses (i.e., limit chronic demyelination) in order to delay the progression from inflammation to neurodegeneration (Vollmer, 2007). Disease-modifying treatments (DMTs) (e.g., Interferon-beta-1a/b) have been approved by the FDA for the prevention of relapses, though such therapies are not effective for reducing brain atrophy (i.e., reducing neurodegeneration) during the progressive stage of MS (Confavreux & Vukusic, 2006; PRISMS Study Group, 1998). Recent studies have identified prominent areas of MS-related neurodegeneration in the brain (i.e., cortical atrophy) that include the cingulate gyrus, and insular, frontal, temporal, and parietal cortices, with less degeneration occurring in the primary motor, sensory, and visual cortices (Trapp & Nave, 2008). Those areas of MS-related cortical atrophy have further been linked with cognitive impairment (Benedict & Zivadinov, 2011).

COGNITIVE DYSFUNCTION IN MS: PREVALENCE, DOMAINS, AND IMPACT

Prevalence of Cognitive Dysfunction in MS

Cognitive impairment is common and debilitating in MS. Based on a review of studies involving neuropsychological testing, an estimated 45-65% of individuals with MS demonstrate cognitive impairment (Benedict & Zivadinov, 2011). Another review highlighted that overall, cross-sectional studies that have been performed in clinical settings have previously estimated that 54-65% of persons with MS are cognitively impaired, whereas community-based studies have reported lower prevalence estimates of cognitive impairment (i.e., 43-46%; Amato, Portaccio, & Zipoli, 2006a). The prevalence of cognitive impairment might vary based on clinical presentation of MS (Amato et al., 2006a; Benedict & Zivadinov, 2011). Cognitive dysfunction is prevalent in the three main clinical disease courses (e.g., RRMS, SPMS, and PPMS), and can often affect individuals in the earliest stages of the disease, even prior to a definite MS diagnosis (i.e., CIS) (Amato et al., 2006a; Denney, Sworowski, & Lynch, 2005; Achiron & Barak, 2006). One recent study reported that approximately 35% of patients with RRMS are cognitively impaired, based on scores at least 1 standard deviation below the normative value on two separate neuropsychological tests (Patti et al., 2009). However, other large studies have reported that approximately 60% of samples that included both persons with relapsing and progressive presentations of MS demonstrated cognitive impairment, based on poor performance on neuropsychological tests (e.g., Benedict et al., 2006b). Other research suggests that although cognitive impairment can occur in CIS (i.e., greater impairment than healthy controls), the prevalence of cognitive impairment is considerably lower than in those with RRMS and SPSMS (Potagas et al., 2008).

Domains of Cognitive Dysfunction in MS

Reviews and meta-analyses have documented that cognitive dysfunction in MS, measured by neuropsychological testing, typically presents as slowed cognitive processing speed, executive dysfunction, and impairments in learning and memory; intellectual functions and language skills are relatively spared (Benedict & Zivadinov, 2011; Bobholz & Rao, 2003; Zakzanis, 2000; Prakash, Snook, Lewis, Motl, & Kramer, 2008). One review described these impairments relative to healthy controls across a variety of methodological paradigms for assessing cognitive function, and further summarized that in general, persons with progressive presentations of MS performed worse on neuropsychological tests of cognitive processing speed, executive function, and learning and memory than persons with RRMS (Bobholz & Rao, 2003).

Three meta-analyses have examined the effects of MS on cognitive function. An early meta-analysis described impairments of similar magnitude in multiple cognitive domains (i.e., general cognitive ability, learning and memory, interhemispheric transfer) across studies of persons with MS (Wishart & Sharpe, 1997). Interestingly, in this quantitative review, disease course was not a significant moderator of the association between MS and domains of cognitive function (Wishart & Sharpe, 1997). A later meta-analysis of cognitive function and MS examined 34 studies, and included a pooled sample of 1,845 persons with MS and 1,265 healthy controls (Zakzanis, 2000). This meta-analysis reported large, negative effects of MS on cognitive processing speed based on SDMT scores ($d = -1.36$) and learning and memory based on scores from the delayed recall portion of the Selective Reminding Task (SRT) ($d = -1.44$), as well as moderate, negative effects on executive function based on performance on the Stroop Color-Word Interference Test ($d = -0.62$) (Zakzanis, 2000). The moderator analysis from this study was not consistent with the results of the previous meta-analysis (Wishart & Sharpe, 1997) such that the impact of slowed processing speed and executive dysfunction was greater in persons

with chronic progressive presentations of MS compared with relapsing-remitting presentations of the disease (Zakzanis, 2000). A third, more recent meta-analysis examined cognitive impairments in individuals with RRMS (Prakash et al., 2008). This meta-analysis examined 57 studies that yielded 755 total effects. Overall, diagnosis of RRMS had a negative effect of moderate magnitude on cognition ($g = -0.59$) (Prakash et al., 2008). The moderator analysis revealed that RRMS had larger, negative effects on the domains of learning and memory ($g = -0.61$) and executive function/attention (namely cognitive processing speed; $g = -0.56$) than on the domains of verbal functioning and language ($g = -0.44$) and concept formation and reasoning ($g = -0.31$) (Prakash et al., 2008). Those core cognitive deficits, including impairments in inhibitory control (i.e., an executive function of interest), have further been associated with cortical atrophy and other structural brain outcomes (e.g., Benedict et al., 2006a; 2013; Genova et al., 2013, Benedict, Bakshi, Simon, Priore, Miller, & Munschauer, 2002; Bagnato et al., 2010; Penner, Rausch, Kappos, Opwis, & Radü, 2003).

Impact of Cognitive Dysfunction in MS

Cognitive impairment is a highly disabling consequence of MS. There is evidence that cognitive impairment has been linked with depression in MS, although this relationship is not fully understood (Arnett et al., 2008). There is some evidence describing associations between slowed cognitive processing speed and executive dysfunction and depression in MS (Rao, Leo, Ellington, Nauertz, Bernardin, & Unverzagt, 1991; Arnett, Higginson, & Randolph, 2001). For example, one longitudinal study reported that processing speed and executive function, based on scores from the Tower of London test, independently predicted 33% of variance in depression scores in 79 persons with MS (Arnett et al., 2001).

Further, cognitive impairment and decline have been associated with unemployment and loss of employment, respectively, in persons with MS (Morrow, Drake, Zivadinov, Munschauer, Weinstock-Guttman, & Benedict, 2010; Benedict et al., 2005). One recent longitudinal study followed 65 newly-diagnosed persons with MS over a 7-year period, and reported that at baseline, approximately 82% of the sample was employed, and at follow-up 7 years later, only 54% of the sample was employed (Ruet et al., 2012). Of those who were not working at follow-up, nearly 80% of participants were cognitively impaired based on neuropsychological test performance (Ruet et al., 2012). To that end, another study established a minimal clinically important difference (MCID) score of 4 on the SDMT as being predictive of employment status in persons with MS (Morrow et al., 2010).

There is further evidence that cognitive impairment in MS is associated with the loss of driving ability (e.g., Shawaryn, Schultheis, Garay, & DeLuca, 2002; Lincoln & Radford, 2008). One exemplar cross-sectional study of 34 persons with MS reported that tests of cognitive processing speed, executive function, and visual memory, in particular, predicted safety to drive, based on performance on a road test (Lincoln & Radford, 2008).

Finally, MS-related cognitive impairment is associated with loss of independence, increased reliance on caregivers, and social isolation. One seminal longitudinal study examined neuropsychological performance and the effects on everyday functioning in 45 persons with MS over a 10-year period (Amato, Ponziani, Siracusa, & Sorbi, 2001). Importantly, over time, decreased performance on a battery of neuropsychological tests, independent of physical disability, predicted loss of independence, increased need for substantial assistance with activities of daily living (i.e., greater than 3 hours per day), and extent of social isolation in persons with MS (Amato et al., 2001).

Strategies for specifically treating cognitive impairment in MS can be classified based on two approaches: pharmacological and non-pharmacological (Amato et al., 2013). This section of the review first discusses the evidence regarding pharmacological approaches for managing cognitive impairment in MS, based on disease modifying therapies (DMTs) and symptomatic treatments. This section then discusses the evidence describing the effects of non-pharmacological approaches (i.e., cognitive rehabilitation) for managing cognitive impairment in MS.

Pharmacological Approaches

DMTs. Currently, there is no FDA-approved pharmacological treatment for cognitive dysfunction in MS (Amato et al., 2013). Disease-modifying agents (e.g., interferon beta-1a, interferon beta-1b, glatiramer acetate, and natalizumab) reduce ongoing CNS inflammatory activity associated with MS pathophysiology, and are hypothesized to reduce cognitive impairment based on this mechanism (Amato et al., 2013). However, overall results from studies linking DMTs to performance on neuropsychological tests have been disappointing, primarily due to methodological limitations, resulting in poor internal validity (Amato et al., 2006a; Amato, Zipoli, & Portaccio, 2006b; Amato et al., 2013). For example, one three-year study of patients with RRMS with mild disability reported that high doses of interferon-beta-1a were associated with a 32% reduction in risk for cognitive decline, based on neuropsychological test performance (Patti et al., 2010). One methodological issue with that study is that there was not an untreated control group or placebo condition to directly quantify the extent to which interferon-beta-1a prevented cognitive decline (Patti et al., 2010).

Another open-label, non-randomized, non-placebo controlled study examined the effects of interferon β-1b on cognitive function compared with a non-treatment control (i.e., passive control) (Barak & Achiron, 2002). After 1 year, patients treated with interferon β-1b demonstrated improved performance on cognitive tests of attention and visuospatial learning; but, there were no treatment effects of the interferon on cognitive processing speed, based on SDMT performance, relative to those in the untreated control condition (Barak & Achiron, 2002). This null result was particularly disappointing given that slowed cognitive processing speed is the most common cognitive impairment among persons with MS, and the SDMT is widely recognized as the most sensitive neuropsychological test of cognitive processing speed in MS (Benedict & Zivadinov, 2011).

The effects of glatiramer acetate (GA) on cognitive function have also been examined in a Phase III clinical trial (Weinstein, Schwid, Schiffer, McDermott, Giang, & Goodman, 1999). Two hundred forty-eight patients initially underwent Rao's Brief Repeatable Battery (BRB) of neuropsychological tests, and were treated with either GA or placebo for 2 years; cognitive testing further was administered at the 12 and 24-month time points, respectively. There were no significant differences in neuropsychological performance between groups at baseline. Both groups demonstrated improvements in cognition overall (i.e., non-significant group × time interactions) at both the 12- and 24-month time points, though the GA group did demonstrate a reduction in disease activity (Weinstein et al., 1999). A recent review suggested that the null results on cognition from the above study might be due to a ceiling effect, based on the sample not demonstrating cognitive impairment at baseline (Amato et al., 2013).

Finally, the effects of natalizumab on cognitive function have not been well-studied in persons with MS. Although there have not been definitive results from Phase III RCTs of

natalizumab on cognitive function in MS, there have been preliminary studies that suggest promising effects of this DMT on cognition (e.g., Portaccio et al., 2013; Mattioli, Stampatori, & Capra, 2011).

Symptomatic Treatments. Pharmacological symptomatic treatments (e.g., L-amphetamine sulfate, modafinil, and donepezil) have been considered as a means to improve cognitive function in individuals with MS to mixed results. L-amphetamine sulfate (i.e., a CNS stimulant) has been associated with enhanced memory in both animal models and humans (Morrow et al., 2009). There further is preliminary evidence to suggest that L-amphetamine sulfate might enhance cognitive processing speed in MS, based on promising findings from a within-subjects trial involving 19 persons with MS (Benedict et al., 2008). However, those results were not replicated in a randomized, double-blind, placebo-controlled trial of 151 cognitively impaired persons with MS (Morrow et al., 2009). In that study, participants received either a 29-day oral dose of 30 mg of L-amphetamine sulfate or placebo, and a battery of neuropsychological tests was administered both before and after the 29-day treatment period for both groups. Disappointingly, results indicated that there were no significant improvements on cognitive processing speed, based on SDMT performance (Morrow et al., 2009).

Modafinil is another potential symptomatic treatment for cognitive impairment in MS, and is a CNS stimulant that was originally designed as an anti-fatigue agent. To date, there is not convincing evidence for its enhancement of cognitive function in MS (Amato et al., 2013; Lovera et al., 2010). For example, one recent double-blind, placebo-controlled RCT examined the effects of a daily 200 mg dose of modafinil (or placebo) for 8 weeks on cognitive processing speed in 121 persons with MS (Möller et al., 2011). There was a significant positive effect of modafinil on SDMT scores relative to the placebo, but not on Paced Auditory Serial Addition

Test (PASAT) scores (i.e., another measure of cognitive processing speed), which actually improved in the placebo group over the 8-week period (Möller et al., 2011).

Donepezil, an acetylcholinesterase inhibitor used to treat dementia in individuals with Alzheimer's disease, has been considered as a potential treatment of cognitive impairment in MS. In a randomized, double-blind, placebo-controlled study, the effectiveness of donepezil on memory function was evaluated in a sample of 69 individuals with MS (Christodoulou, Melville, Scherl, MacAllister, Elkins, & Krupp, 2006). Participants received treatment for 24 weeks with either donepezil or a placebo and completed the SRT at both baseline and at the completion of the treatment course (Christodoulou et al., 2006). Results indicated that patients receiving donepezil significantly improved memory function to a medium effect size compared with the placebo group (Christodoulou et al., 2006). However, a recent multi-center double-blind, placebo-controlled RCT did not replicate those results, such that there was not a significant effect of donepezil on SRT performance (Krupp et al., 2011).

The generally equivocal results from studies examining L-amphetamine sulfate, modafinil, and donepezil might be due to methodological limitations. Perhaps those studies did not include the optimal neuropsychological outcome measure based on each drug's biological mechanism for evaluating the effectiveness of those treatments. Another plausible explanation is that those studies might not have optimized the dosage of each treatment for maximal effects on cognitive functioning. A third potential explanation might involve selection biases, as the effectiveness of those treatments might depend on level of cognitive impairment (Amato et al., 2013). Clearly, more research on symptomatic pharmacological treatments of cognitive impairment in MS is needed with stronger experimental designs involving larger sample sizes (Amato et al., 2006b; 2013).

Non-Pharmacological Approaches

Non-pharmacological treatment of cognitive impairment in MS primarily involves cognitive rehabilitation. Cognitive rehabilitation interventions are designed to either directly improve cognition or develop strategies to compensate for cognitive impairment, and can often include psychotherapy for addressing issues that can indirectly affect cognitive impairment (e.g., depression, personality difficulties; Amato et al., 2013; Bobholz & Rao, 2003; Chiaravalloti & DeLuca, 2008). In general, 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 (O'Brien, Chiaravalloti, Goverover, & DeLuca, 2008; Chiaravalloti & DeLuca, 2008). However, there are recent data that seemingly support cognitive rehabilitation interventions in persons with MS (Amato et al., 2013). Though this line of research is in its infancy, there have been several studies and reviews examining the effects of cognitive rehabilitation on specific cognitive domains.

The vast majority of successful cognitive rehabilitation interventions in MS have focused on learning and memory. One promising double-blind, placebo-controlled RCT examined the effect of a 5-week cognitive rehabilitation training program on memory in 29 persons with MS. This training program involved the use of imagery and context to aid new learning (Chiaravalloti, DeLuca, Moore, & Ricker, 2005). Those who were randomly assigned to the training program demonstrated improvements in memory based on self-report and performance on neuropsychological tests relative to those who underwent the placebo condition (i.e., non-specific memory exercises; Chiaravalloti et al., 2005). Further, a recent study replicated this intervention in 8 persons with MS and reported that persons who underwent imagery and context training demonstrated significantly increased blood oxygen level dependent activation of frontal

and parahippocampal brain regions during a functional MRI (fMRI) memory task compared with those who underwent the placebo training condition (Chiaravalloti, Wylie, Leavitt, & DeLuca., 2012).

The evidence supporting cognitive rehabilitation interventions for improving cognitive processing speed and executive functioning in MS is far less convincing than for learning and memory (Amato et al., 2013). In fact, there are no published cognitive rehabilitation interventions for specifically improving cognitive processing speed, as highlighted by one recent review (Amato et al., 2013). There further is equivocal evidence supporting cognitive rehabilitation interventions for improving executive functioning. This is largely based on the lack of definitive evidence for targeted executive function training interventions for specifically improving executive functioning in persons with MS. However, there seems to be more convincing support for generalized cognitive rehabilitation on executive functioning in this population (Amato et al., 2013). One double-blind, controlled study examined the effects of a 3-day per week generalized computerized training program on executive function over a 3 month period in 20 persons with MS (Mattioli, Stampatori, Zanotti, Parrinello, & Capra, 2010). This study reported improvements in executive function, based on PASAT and Wisconsin Card Sorting Task scores for the intervention group, compared with an untreated control condition (Mattioli et al., 2010).

Collectively, there is some evidence to support pharmacologic and non-pharmacologic treatments for mitigating cognitive impairment in MS; however, there is not yet overwhelming support for either approach (Amato et al., 2013). This highlights the need for examining alternative behavioral approaches for managing cognitive dysfunction in persons with MS. One such approach involves exercise training.

Exercise training might represent a behavioral approach for managing cognitive dysfunction in persons with MS, but this area has been understudied. There is emerging interest by researchers and clinicians in the effects of exercise (i.e., planned behavior aimed towards improving an individual's fitness), fitness (i.e., characteristics of an individual, reflecting aerobic capacity, muscular strength, balance, body composition, etc.) and physical activity (i.e., skeletal muscle contraction resulting in increased energy expenditure) on cognition in individuals with MS. To that end, this section of the review provides a brief history of the evidence of exercise training, fitness, and physical activity effects on cognitive function in MS, based on publication date. This brief history provides critical background information for the development of a line of research on exercise training and cognition in MS (e.g., Motl et al., 2011) that includes the current study.

Two initial RCTs examined the effects of exercise training on cognition in persons with MS. The first RCT involved a six-month intervention consisting of a weekly yoga class, weekly aerobic exercise class, or wait-list control condition in 57 individuals with mild MS disability (mean Expanded Disability Status Scale (EDSS) score = 2.9; Oken et al., 2004). Participants were randomized to the yoga, aerobic exercise, or control group. The yoga intervention consisted of a 90-minute session of Iyengar yoga, adapted for persons with MS, taking place once per week. The aerobic exercise intervention entailed group exercise on a stationary bicycle at the intensity of 2-3 on the Borg Rating of Perceived Exertion (RPE) scale (i.e., minimal exertion); sessions took place once per week, and home exercise was encouraged (Oken et al., 2004). Periodically, participants were given the option of exercising on a Swiss ball rather than cycling.

Cognition was measured prior to and following the six-month period using a battery of neuropsychological tests that mainly captured various aspects of attention, cognitive processing speed, and executive function. Following the completion of the intervention, neither the yoga group nor the exercise group demonstrated significant improvements in any cognitive measure (e.g., Stroop Color-Word Interference Test, PASAT) compared with the wait-list control group (Oken et al., 2004).

Importantly, there are some methodological concerns with that study. One concern is that the aerobic exercise intervention was conducted at an extremely light intensity (e.g., 2-3 on the Borg RPE scale) as well as occurring only once per week, such that the maximal benefits of exercise training on cognition could not be realized. In fact, the aerobic exercise stimulus was not frequent nor intense enough to meet public health guidelines for accruing general health benefits (i.e., resulting in less than 150 minutes of moderate-to-vigorous physical activity per week) (American College of Sports Medicine (ACSM), 2013). 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. This methodological concern was compounded by the absence of an intervention effect on physical fitness. Physical fitness is a key manipulation check for gauging the success of any exercise training intervention (e.g., Motl et al., 2013), and this lack of a manipulation check further brings into question the effectiveness of the exercise stimuli for optimally benefitting cognitive function in MS.

The other early RCT of exercise training on cognition in MS involved 95 persons with mild MS disability (median EDSS = 2.0) who were randomized into either a six-month long

exercise training intervention or wait-list control group (Romberg, Virtanen, & Ruutiainen, 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 et al., 2005). This part of the program, prescribed by physiotherapists, entailed mostly resistance exercise (i.e., suggested to take place 3-4 times per week) with additional sessions of aerobic exercise (i.e., suggested to take place once per week) (Romberg et al., 2005). Participants were encouraged via phone to adhere to the home exercise program on four separate occasions over the six-month intervention (Romberg et al., 2005). Cognition was measured prior to and following the six-month period using only the PASAT. Accordingly, cognitive processing speed did not significantly improve in persons with MS who underwent the exercise intervention (Romberg et al., 2005).

One similar concern about the results of this RCT is that physical function did not significantly improve in the exercise group over the six-month period ($ES = -0.19$), indicating that the exercise prescription was ineffective (Romberg et al., 2005). Additionally, physical function was assessed through a self-reported measure of quality of life (MSQOL-54), rather than with an objective performance measure (i.e., aerobic capacity). Given that this exercise stimulus largely consisted of resistance training, a major study limitation is that there was no measure of muscular strength that was administered prior to and following the intervention. A possible factor for the lack of improvement of physical function (and possibly cognitive processing speed) 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).

As results from the first two RCTs of exercise training on cognition in MS were disappointing, perhaps due to methodological concerns, several studies then examined the cross-sectional effects of physical fitness (a presumed surrogate for exercise training) on cognition (i.e., primarily cognitive processing speed) in MS to better inform subsequent RCTs. The first cross-sectional study examined the association between cardiorespiratory fitness (i.e., aerobic capacity) and cognition, as well as cortical activation patterns using fMRI in 24 individuals with mild MS disability (mean EDSS = 2.6; Prakash et al., 2007). Cardiorespiratory fitness was assessed using an incremental exercise test to exhaustion on a cycle ergometer in order to measure aerobic capacity, based on peak oxygen consumption (VO_{2peak}) (Prakash et al., 2007). Cognition was assessed using Rao's BRB (i.e., SRT, Spatial Recall Test, PASAT, SDMT, and a word-list generation task), as well as with the PVSAT, a fMRI paradigm that is based on the PASAT (Prakash et al., 2007). Results indicated that greater aerobic capacity was significantly correlated with shorter RT on the PVSAT and higher scores on the PASAT, but not scores on measures of learning and memory (i.e., SRT) (Prakash et al., 2007). Additionally, higher aerobic capacity was associated with greater activation of the right inferior frontal gyrus and middle frontal gyrus, and less activation of the anterior cingulate cortex during the PVSAT (Prakash et al., 2007). This pattern of neural activation in persons with MS is similar to the pattern of activation observed during successful completion of an executive control task in high fit older adults and healthy young adults (Colcombe et al., 2004).

A later cross-sectional study examined the relationship between aerobic capacity, white and grey matter integrity, and cognition in a sample of 21 persons with mild MS disability (mean EDSS = 2.2) and 15 healthy controls (Prakash, Snook, Motl, & Kramer, 2010). All participants underwent an incremental exercise test to exhaustion on a cycle ergometer for measurement of

aerobic capacity (i.e., VO_{2peak}). Participants also underwent Rao's BRB of neuropsychological tests. Finally, in order to evaluate white and grey matter integrity, participants underwent MRI using lesion-load analysis, voxel-based morphometry (VBM), and diffusion tensor imaging (DTI) (Prakash et al., 2010). Briefly, there were significant differences in aerobic capacity, measures of cognitive processing speed, and MRI outcomes between persons with MS and healthy controls (i.e., Cohen's $d > 0.67$). In the MS subsample, higher aerobic capacity was associated with better performance on a composite measure of cognitive processing speed, but not on tests of learning and memory. This is consistent with results from the previous cross-sectional study of fitness and cognition in MS (Prakash et al., 2007). A novel result from this study was that in the MS subsample, higher aerobic capacity was associated with less lesion-load volume, greater grey matter volume, and greater white matter integrity (i.e., greater fractional anisotropy in the left posterior thalamic radiation and right anterior corona radiata; Prakash et al., 2010). The collective results from that study suggest that aerobic capacity, cognitive processing speed, and brain measures of white and grey matter integrity are interrelated in persons with mild MS disability (Prakash et al., 2010).

The third, more recent cross-sectional study examined the relationships among multiple domains of physical fitness (e.g., aerobic capacity, muscle strength asymmetry, and balance) and cognitive processing speed in 31 persons with mild MS disability (median Patient-Determined Disease Steps (PDDS) score = 2) and 31 controls matched by age, sex, height, and weight (Sandroff & Motl, 2012). Aerobic capacity was measured as peak oxygen consumption (VO_{2peak}) using an incremental exercise test to exhaustion on a cycle ergometer; lower limb muscle strength asymmetry (i.e., relative difference in the strength of a particular muscle group between strong and weak limbs) was measured using an isokinetic dynamometer; balance was measured

using static posturography. Cognitive processing speed was expressed as a composite *z*-score based on performance on the SDMT and PASAT (Sandroff & Motl, 2012). Briefly, there were significant differences in measures of fitness and cognition between persons with MS and matched controls that were moderate-to-large in magnitude. In the MS subsample, worse aerobic capacity (r = .44), worse balance (i.e., larger postural sway area) (r = −.52), and greater knee extensor asymmetry (r = −.39) were significantly associated with slower cognitive processing speed. Additional noteworthy results from that study were that those three domains of fitness accounted for differences in cognitive processing speed between persons with MS and controls, and explained a statistically significant amount of variance in cognitive processing speed (R^2 = .39) in the MS subsample (Sandroff & Motl, 2012).

Collectively, the cross-sectional results from studies of physical fitness and cognition in MS seemingly indicate that physical fitness is associated with cognitive processing speed, but not learning and memory in persons with mild MS disability. This suggests that enhancing aerobic capacity, balance, and muscular strength might represent avenues for improving slowed cognitive processing speed in this population. Importantly, results from cross-sectional studies of fitness and cognition, described above, are not consistent with the null results from previous RCTs of exercise training and cognition in MS. Despite the null results of the early RCTs, the cross-sectional research on fitness and cognition seems to suggest potential benefits of aerobic exercise, and perhaps resistance and balance exercise, on cognitive processing speed in persons with MS.

One recent RCT recognized the importance of physical fitness and examined the effects of a supervised, aerobic exercise training intervention on fitness and cognitive function in 42 persons with progressive MS who had moderate disability (mean EDSS = 4.95; Briken et al.,

2014). Participants were randomized to one of three aerobic exercise training conditions (i.e., arm ergometry, rowing, cycle ergometry) or a wait-list control condition. All participants underwent an incremental exercise test to exhaustion to determine cardiorespiratory fitness at baseline and again at follow-up. Further, all participants underwent a battery of neuropsychological tests for measuring cognitive processing speed, verbal learning and memory, attention, and executive function at baseline and follow-up. The exercise training sessions took place 2-3 times per week for 15-45 minutes per session over 8-10 weeks; the exercise intensities per session were prescribed based on percentage of aerobic threshold demonstrated during the baseline incremental exercise test (Briken et al., 2014).

Persons who underwent cycle ergometer training, but not rowing training, arm ergometer training, or wait-list control conditions demonstrated significant improvements in cardiorespiratory fitness. Those who underwent cycle ergometer training further demonstrated concomitant improvements in verbal memory and alertness, but not in cognitive processing speed or executive function, compared with the wait-list control group. Those changes in fitness explained ~16% of variance in changes in verbal memory and alertness within the cycle ergometry condition (Briken et al., 2014).

The results from the recent exercise training RCT are promising, as that study reported improvements in physical fitness following the cycle ergometer training, along with significant improvements in verbal learning and memory in persons with progressive MS and moderate disability. This further has been replicated in a case study involving two memory-impaired persons with MS (Leavitt et al., 2014). However, those results still were not in-line with those from cross-sectional studies of fitness and cognition in MS, such that there were not improvements in cognitive processing speed following either exercise training intervention. This

might be attributable to disability status, as the sample from the recent RCT had substantially worse disability compared with the cross-sectional samples. Indeed, there have been two published studies on physical activity behavior and cognitive processing speed in persons with MS that have examined disability as a potential moderating factor of the physical activity/cognition relationship (Sandroff et al., 2013; 2014).

One prospective study examined physical activity and cognition in 78 persons with mild and moderate MS disability (Sandroff et al., 2013). At baseline, physical activity was measured objectively using accelerometers, and was expressed as steps/day. After a six-month period without intervention, participants underwent neuropsychological assessments of cognitive processing speed, consisting of both oral and written versions of the SDMT, and the PASAT (Sandroff et al., 2013). After controlling for age, sex, and self-reported disability status in the overall sample, steps/day was significantly associated with cognitive processing speed based on oral and written SDMT scores (pr_s = .25-.29); steps/day was not significantly associated with performance on the PASAT (pr_s = .12). Importantly, the researchers split the overall sample into two groups of mild and moderate disability based on scores from a self-reported EDSS (SR-EDSS) in order to examine the role of disability status as a potential moderator of the association between steps/day and cognitive processing speed. After controlling for age, steps/day was associated with cognitive processing speed (based on oral and written SDMT scores) in persons with mild (SR-EDSS < 4.0; pr_s = .35-.36), but not moderate (SR-EDSS ≥ 4.0; pr_s = .24-.27) MS disability (Sandroff et al., 2013).

Another study used a RCT design to examine the effects of a six-month, Internet-based behavioral physical activity intervention on cognition in 76 persons with mild and moderate MS disability (Sandroff et al., 2014). All participants completed the International Physical Activity

Questionnaire (IPAQ; a self-report measure of physical activity that is valid in persons with MS) and underwent the oral version of the SDMT at baseline and follow-up. Participants were randomized to either the physical activity intervention or wait-list control condition. The intervention condition involved visiting a study website that was based on social cognitive theory; wearing a pedometer, completing a log-book, and using computerized software for guiding goal-setting and attainment; and participating in one-on-one video chat sessions with a behavior-change coach (Sandroff et al., 2014).

Following the six-month period, persons with mild disability (PDDS = 0-2) in the intervention condition reported large increases in physical activity (i.e., Cohen's d = 1.63), whereas those with moderate disability (PDDS = 3-6) in the intervention condition reported a small increase in physical activity relative to baseline (Cohen's d = 0.24). The most important result from this study was that persons who underwent the intervention condition with mild MS disability demonstrated a clinically meaningful improvement in SDMT scores (~6 point increase), whereas those with moderate MS disability who underwent the intervention condition demonstrated minimal change (~1 point decrease) in SDMT scores. There were no changes in physical activity or cognitive processing speed over the six-month period for those who were randomized to the wait-list control condition. Further, among persons in the intervention condition, changes in average steps/day from the pedometer (i.e., objectively-measured physical activity) were associated with changes in SDMT scores in persons with mild (ρ = .52), but not moderate (ρ = .09) MS disability (Sandroff et al., 2014).

Following the publication of the poorly-designed early RCTs (i.e., Oken et al., 2004; Romberg et al., 2005), there seems to be an emerging pattern of results from cross-sectional studies of fitness, a recent RCT involving exercise training, and studies of physical activity and

cognitive function. That pattern of results suggests that different domains of exercise training and fitness might be associated with different domains of cognitive function. Those associations further might depend on disability status. To clarify that previous research, we recently completed a cross-sectional study that directly examined multiple domains of physical fitness (i.e., aerobic capacity (cardiorespiratory fitness) and muscular strength) and multiple domains of cognition (i.e., cognitive processing speed and learning and memory) in a relatively large sample of persons with mild, moderate, and severe MS disability (i.e., N=62) (Sandroff et al., 2015b). Briefly, aerobic capacity was measured as VO_{2peak} from an incremental exercise test to exhaustion on a recumbent stepper, and lower limb muscle strength was expressed as peak torque of knee extensors and flexors, as well as asymmetry scores based on a maximal isometric muscle strength protocol on an isokinetic dynamometer. Participants also underwent the Brief International Cognitive Assessment in Multiple Sclerosis (BICAMS) neuropsychological battery, which consists of the oral version of the SDMT as a measure of cognitive processing speed, the California Verbal Learning Test-2 (CVLT-2) as a measure of verbal learning and memory, and the Brief Visuospatial Memory Test-Revised (BVMT-R) as a measure of visual learning and memory (Sandroff et al., 2015b).

In the overall sample, measures of aerobic capacity and lower-limb muscle strength were associated with cognitive processing speed (r = .35-.41), but not learning and memory (r < .19). Similar to our previous examinations of physical activity and cognition (Sandroff et al., 2013; 2014), disability status moderated those associations such that aerobic capacity and muscle strength were associated with cognitive processing speed in persons with mild (EDSS 0-3.5; r = .39-.53), but not moderate (EDSS 4.0-5.5) or severe (EDSS 6.0-6.5) MS disability (r < .21) (Sandroff et al., 2015b). Further, a *post-hoc* stepwise linear regression analysis indicated that

aerobic capacity, but not muscular strength outcomes, independently explained a statistically significant portion of variance (i.e., 17%) in SDMT scores. Results from this study provided direct, preliminary evidence of a selective association of physical fitness and cognitive function domains in persons with MS. Namely, cardiorespiratory fitness, and to a lesser extent lower limb muscle strength, is associated with the specific domain of cognitive processing speed, particularly among those with mild disability. This supports the design and implementation of an aerobic exercise training intervention for improving cognitive processing speed, but not learning and memory, in persons with mild MS disability.

Overall, the research examining exercise training, fitness, physical activity and cognition in MS is clearly in its infancy. The disappointing results from early training studies, along with the growing pattern of results from recent studies of exercise, fitness, physical activity, and cognition in MS highlight the importance of considering the well-established literature in the general population across the lifespan (Hillman et al., 2008) as well as preliminary evidence from other neurological populations (McDonnell et al., 2011) as a way of better informing examinations of exercise training and cognition in MS.

EXERCISE TRAINING AND COGNITION IN OTHER POPULATIONS

There is a wealth of evidence describing robust effects of exercise training on cognitive functioning in the general population across the lifespan (i.e., children, younger adults, and older adults) (Voss, Nagamatsu, Liu-Ambrose, & Kramer, 2011). There further is preliminary evidence regarding the beneficial effects of exercise on cognitive function in persons with neurological disorders (i.e., schizophrenia, stroke, TBI), though the number of RCTs in those populations is substantially smaller than in healthy children, younger adults, and older adults. To

that end, this section of the review highlights meta-analyses, reviews, and exemplar RCTs to describe the overall effects of exercise training on cognition in healthy children, younger adults, and older adults, given the large body of literature. Given the lack of meta-analyses on the effects of exercise training on cognition in persons with neurological disorders, this section of the review primarily highlights RCT results in those populations. The *acute* effects of exercise on cognition in the general population are not discussed in this section, but rather, in the following section. The literature involving exercise training and cognitive functioning in healthy children, younger adults, older adults, respectively, as well as in persons with neurological disorders, provides a backdrop for informing the development of a well-designed RCT of exercise training on cognition in persons with MS.

Exercise and Cognition in Children

There has been increasing interest in the effects of exercise on cognition in children, though this relationship has primarily been studied in older adults, given the prevalence of cognitive impairment in those over 65 years of age. Compared with the gerontology literature, there are substantially fewer studies of exercise and cognition in children; however, the overall effects of physical activity on cognitive function in this population have been previously summarized. One early meta-analysis examined 125 effect sizes from 44 studies and reported that physical activity was associated with improved cognitive performance in children, with an overall effect size of 0.32 standard deviations (Sibley & Etnier, 2003). Importantly, the type of cognitive assessment emerged as a significant moderator variable, with the largest effects occurring for tests of perceptual skills (*ES* = 0.49) and the smallest effects for tests of memory (*ES* = 0.03). Age group was another moderator of the physical activity/cognition association with larger effects occurring in young elementary-school aged children (*ES* = 0.48) and middle-school

aged children (*ES* = 0.48) (Sibley & Etnier, 2003). A third noteworthy result from this meta-analysis was that the authors identified a lack of true RCTs (at the time of publication) that could better support a causal association of exercise and cognition in children (Sibley & Etnier, 2003).

Since the publication of that pivotal meta-analysis, there have been several well-designed RCTs that have reported improvements in executive control, in particular, in response to an exercise training intervention (e.g., Davis et al., 2007) that have been summarized in a review (Best, 2010). A more recent RCT (i.e., published after the Best review) examined the effect of a 9-month long exercise intervention (i.e., the FITKids intervention) on executive control in 23 8- and 9-year old children (Chaddock-Heyman et al., 2013). Children were randomized to either an exercise intervention condition or wait-list control condition. The exercise intervention involved 120 minutes per day of moderate-to-vigorous physical activity based on non-competitive games and aerobic fitness activities, for 5 days per week. Executive control was measured prior to and following the 9-month period based on outcomes on the modified flanker task. Following the 9-month period, children randomized to the exercise intervention demonstrated improvements in executive control based on percent accuracy on incongruent trials of a modified flanker task relative to children randomized to the wait-list control condition (Chaddock-Heyman et al., 2013). Importantly, at follow-up, children who participated in the intervention demonstrated accuracy rates similar to those of healthy young adults (Chaddock-Heyman et al., 2013). This study provides an example of how a well-designed exercise stimulus can selectively improve executive control in children. Of note, other recent investigations have reported improvements in memory and concomitant improvements in brain structure and function (e.g., Monti, Hillman, & Cohen, 2012; Chaddock et al, 2010) following the FITKids intervention.

Exercise Training and Cognition in Healthy Adults

There is a relative paucity of literature directly examining exercise training on cognition in healthy younger adults, compared with the respective bodies of literature on children and older adults. This might be due to cognitive performance peaking during younger adulthood, presumably minimizing the potential for improvements in cognitive functioning following exercise (Hillman et al., 2008). Rather, younger adults tend to comprise control comparison groups in studies primarily examining exercise training and cognition in older adults. To date, there is not meta-analytic evidence to describe the overall effects of exercise training on cognition in younger adults only; however, one recent meta-analysis summarized the effects of exercise training on cognition in adults over 18 years of age (Smith et al., 2010). This meta-analysis examined 234 effect sizes from 29 different studies involving both younger and older adults, and reported overall modest effects of aerobic exercise training on attention/processing speed (g = 0.16) and executive function (g = 0.12) (Smith et al., 2010). Although this meta-analysis did include a substantial number of studies involving older adults, age was not a significant moderator of the associations among exercise training, attention/processing speed, and executive function (Smith et al., 2010). This seemingly indicates that across the span of adulthood, exercise training is similarly associated with improvements in attention/processing speed and executive function.

Despite the lack of a meta-analysis to quantify the overall effects of exercise training on cognitive function in only younger adults, several longitudinal studies have examined those effects specifically within this age group. One longitudinal study reported statistically significant improvements in verbal learning and concomitant increases in cerebral blood volume in the hippocampus (i.e., dentate gyrus) following 12 weeks of aerobic exercise training in 11 healthy, but low-fit adults (age range: 21-45) (Pereira et al., 2007). One prospective study examined

whether changes in cardiorespiratory fitness from age 15 to 18 predicted cognitive functioning at age 18 in over 1 million Swedish young adults (Åberg et al., 2009). Importantly, improvements in cardiorespiratory fitness over 3-years were associated with increased global intelligence compared with those whose cardiorespiratory fitness worsened over that timespan (Åberg et al., 2009). Another recent study examined the effects of aerobic exercise training on cognitive function (i.e., face-name matching task and Stroop color-word interference task performance) in 47 healthy male students using a RCT design (Griffin, Mullally, Foley, Warmington, O'Mara, & Kelly, 2011). Participants were randomized to an exercise training intervention or sedentary control condition. The aerobic exercise condition consisted of 3 or 5 weeks of 60 minutes of aerobic cycling exercise that was performed at an intensity of 60% VO_{2max} per session (Griffin et al., 2011). Importantly, persons undertaking 5 weeks of aerobic exercise demonstrated significantly better face-name matching performance compared with those in the control condition; there were no effects of exercise on Stroop performance (Griffin et al., 2011). This study provides an example of exercise training improving memory functions in healthy younger adults. However, given the overall dearth of exercise training RCTs on cognition within this population, compared with children and older adults, those results might not be broadly generalizable.

Exercise Training and Cognition in Healthy Older Adults

There is a large body of literature that documents robust, beneficial effects of exercise training on cognitive function in older adults (i.e., adults over 65 years of age). Early exercise training interventions reported that older adults, following participation in an exercise program, demonstrated improvements in physical fitness and better performance on cognitive tasks compared with controls (e.g., Dustman et al., 1984; Hawkins, Kramer, & Capaldi, 1992). For

example, a classic RCT examined the effect of a six-month long aerobic exercise intervention on executive control, based on performance on several tasks of executive control (i.e., task-switching test, flanker task, stop-signal task) in 124 sedentary older adults (age range 60-75) (Kramer et al., 1999). Participants were randomized to either the aerobic exercise intervention condition (i.e., walking) or a stretching-and-toning control condition. Importantly, all participants underwent a maximal exercise test and the three executive control tests at baseline and follow-up to measure changes in cardiorespiratory fitness and cognition, respectively, over the six-month period (Kramer et al., 1999). Those in the intervention condition demonstrated a 5.1% improvement in cardiorespiratory fitness, whereas those in the control condition demonstrated small decreases (i.e., -2.8%) in cardiorespiratory fitness. Further, those in the intervention condition demonstrated significant improvements in executive control based on better performance on the task-switching, flanker, and stop-signal tasks, particularly for conditions that required greater levels of executive control, relative to those in the control condition at follow-up (Kramer et al., 1999). Those results seemingly indicated that exercise might have a selective benefit on executive control processes in older adults. Selective improvements in executive control have since been replicated in a number of well-designed exercise training interventions involving older adults. The selective effects of exercise training on executive control have more recently been accompanied by concomitant changes in brain structure and function in this population (Voss et al., 2011).

The overall effects of exercise training on cognition in older adults have been summarized by several meta-analyses (e.g., Colcombe & Kramer, 2003; Heyn, Abreu, & Ottenbacher, 2004). One seminal meta-analysis examined 18 studies that yielded 197 effect sizes, and reported that exercise training in healthy older adults was associated with overall

better performance on cognitive tasks with an average effect size of 0.48 standard deviations (Colcombe & Kramer, 2003). This meta-analysis confirmed the selective benefit of exercise training on cognition, such that the largest beneficial effects of exercise occurred for executive control processes (g = 0.68) compared with other cognitive processes (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 (i.e., g = 0.59 vs. 0.41, respectively) (Colcombe & Kramer, 2003). Another meta-analysis examined 30 studies that yielded 85 effect sizes and 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 0.57 standard deviations (Heyn et al., 2004). That meta-analysis did not report a moderator analysis to determine whether exercise training had a selective effect on specific cognitive domains in older adults with documented cognitive impairment.

The large body of literature in the general population, across the lifespan, indicates that exercise training might benefit cognition, particularly executive control processes, in healthy children, younger adults, and older adults. This is critical for informing the development of exercise training studies for improving cognition in other populations. Based on the equivocal results from the exercise training studies on cognition in MS, it is important to examine whether the literature from other neurological populations supports exercise training for improving cognitive function. If so, this would provide support for the feasibility of such a trial in MS. Indeed, there is preliminary evidence that aerobic exercise training might be beneficial for improving cognitive function in persons with neurological disorders (McDonnell et al., 2011).

Exercise Training and Cognitive Function in Persons with Neurological Disorders

There is emerging evidence that exercise training might improve cognitive function in persons with schizophrenia. Schizophrenia is a psychiatric illness that might be linked to the dysfunction of dopamine and other neurotransmitters in the brain. This dysfunction results in the brain's decreased capacity to respond to stimuli via its usual inhibitory mechanisms (Freedman, 2003). Those changes in brain function typically manifest as auditory hallucinations and delusions, as well as cognitive dysfunction (i.e., deficits in sustained attention and impaired short-term verbal and visual memory, in particular) (Freedman, 2003).

One recent RCT examined the effect of an aerobic exercise training intervention on learning, memory, and hippocampal volume (i.e., a brain area implicated in learning and memory processes) in persons with schizophrenia (Pajonk et al., 2011). Sixteen persons with schizophrenia were randomized to either a 12-week aerobic exercise intervention condition or 12-week non-exercise control condition. The aerobic exercise training condition involved 30 minutes of cycling exercise 3 times per week (intensity was based on heart rate associated with a blood-lactate level of 14-18 mg/dL derived from a baseline maximal exercise test), whereas the non-exercise control condition consisted of 30 minutes of foosball, 3 times per week. This study further included 8 healthy control participants, who were matched based on demographic, cognitive, and fitness characteristics to those with schizophrenia; control participants also completed the aerobic exercise intervention (Pajonk et al., 2011). All participants underwent a maximal exercise test to determine aerobic capacity, the Rey Auditory Verbal Learning Test to assess verbal learning and memory, and an MRI to determine hippocampal volume at baseline and follow-up. There was a significant interaction of group across time on Rey Auditory Verbal Learning Test scores, such that persons with schizophrenia who were randomized to the aerobic

exercise condition demonstrated significant improvements in verbal learning and memory relative to persons with schizophrenia randomized to the non-exercise control condition (η^2 = 0.26). Those with schizophrenia who underwent the aerobic exercise intervention demonstrated statistically significant increases in relative hippocampal volume (i.e., 12%) compared to those with schizophrenia who underwent the non-exercise control condition (i.e., 1% decrease in relative hippocampal volume). Among persons with schizophrenia randomized to the aerobic exercise intervention, changes in cardiorespiratory fitness were strongly associated with changes in hippocampal volume (r = .71) (Pajonk et al., 2011). The primary results from this study provide support for aerobic exercise training for improving cognitive function and brain structure in persons with schizophrenia.

There is emerging evidence that might support exercise training for improving cognitive functioning in persons with TBI (McDonnell et al., 2011). Typically, mild TBI involves short-term cognitive dysfunction without the presentation of neuroimaging abnormalities (Fogelman & Zafonte, 2012). One recent review indicated that there is minimal evidence that definitively supports exercise training for improving cognitive function in persons with TBI. This is based on the largely heterogeneous expression of cognitive symptoms and the severity of injuries in persons with TBI (Fogelman & Zafonte, 2012). One promising longitudinal study examined the effects of exercise training on cognition in 13 persons with mild TBI (i.e., ambulatory, without severe cognitive impairment) using a 4-week virtual reality-based exercise stimulus (Grealy, Johnson, & Ruston, 1999). Participants exercised on a cycle ergometer equipped with a virtual reality screen that presented either a Caribbean island course, a countryside course, or a cross-country snow course, and cycled at a moderate intensity (i.e., 10-12 on Borg RPE scale) for 25 minutes per session, 3 times per week. Cognition was measured using a battery of

neuropsychological tests that included measures of processing speed, executive function, learning, and memory that was administered pre- and post-intervention (Grealy et al., 1999). Persons with TBI increased their cycling distance by approximately 2 miles over the 4-week intervention. That training effect was accompanied by statistically significant improvements in processing speed, verbal learning and memory, and visual learning and memory (Grealy et al., 1999). However, one limitation of that study was the lack of non-virtual reality exercise, and non-exercise virtual reality comparison groups of persons with TBI. This could have provided stronger evidence to dissociate the effects of virtual reality from aerobic exercise on cognition in this population.

There further is preliminary evidence that supports aerobic exercise for improving cognitive function in persons with stroke (McDonnell et al., 2011). Upwards of 60% of persons with stroke demonstrate slowed information processing speed and executive dysfunction based on neuropsychological testing (Barker-Collo & Feigin, 2006). Recently, one pilot RCT examined the effects of an 8-week aerobic exercise intervention on information processing speed and executive function in 38 post-stroke survivors (Quaney et al., 2009). Participants were randomized to an exercise intervention condition that consisted of progressive cycle ergometry up to 70% HR_{max}, 3 times per week, or a home-based stretching and toning control condition. Information processing speed was measured using the Serial Reaction Time Test (SRTT) and executive function was measured using the Wisconsin Card Sorting Task, Stroop color-word interference task, and Trail-Making Tests A and B. All participants underwent a maximal exercise test to measure aerobic capacity, as well as the battery of neuropsychological tests at baseline and again at follow-up (Quaney et al., 2009). There was a statistically significant increase in aerobic capacity demonstrated by those randomized to the intervention condition,

compared with those randomized to the control condition, which supported the effectiveness of the exercise stimulus. Importantly, there was a large, statistically significant improvement in RT based on the SRTT in stroke survivors in the intervention group compared with stroke survivors in the control group (d = 0.91). There were not statistically significant improvements on any other neuropsychological test for those in the intervention group relative to those in the control group (Quaney et al., 2009). The authors attributed this latter result to classical neuropsychological testing perhaps lacking the sensitivity to detect exercise-related changes in neurocognitive performance in persons with stroke (Quaney et al., 2009). Of note, more complex measures of cognitive functioning (i.e., computerized neurocognitive measures of executive control) were not collected in this study to examine the potential general (i.e., effects on simple information processing speed) or selective (i.e., effects on inhibitory control/response inhibition) effects of exercise training on cognition, as described in older adults of the general population (e.g., Colcombe & Kramer, 2003).

A recent longitudinal study extended those results by examining the effects of a six-month aerobic and resistance exercise training intervention on cognitive performance in 41 persons with stroke (Marzolini, Oh, McIlroy, & Brooks, 2012). Participants underwent a once-weekly exercise class for 90 minutes over a six-month period. The exercise class consisted of combined aerobic exercise (i.e., walking, cycle/arm ergometery) and resistance training (i.e., upper and lower extremity resistance exercises). Cognitive function was measured by the Montreal Cognitive Assessment—a neuropsychological battery that includes tests of executive function, attention, and learning and memory—pre- and post-intervention (Marzolini et al., 2012). Following the six-month intervention, participants demonstrated improvements in aerobic capacity as well as muscular strength ($p < .001$). Further, participants demonstrated large,

statistically significant improvements on tests of executive function and attention ($p < .03$), but not learning and memory ($p = .40$) (Marzolini et al., 2012). This suggests that perhaps different modes of exercise training have differential effects on cognitive function in persons with stroke (Marzolini et al., 2012).

Recent evidence from persons with neurological disorders does seem to support the feasibility of a well-designed RCT for improving cognition in persons with MS, although the optimal exercise stimulus for such a trial is unknown. Importantly, the delineation of exercise stimuli for largely successful interventions across the lifespan in the general population (and to a lesser extent in persons with neurological disorders) is, in part, based on examinations of the effects of acute bouts of aerobic exercise on cognition (e.g., Tomporowski, 2003; Lambourne & Tomporowski, 2010; Chang et al., 2012).

ACUTE EXERCISE AND COGNITION

There is a growing body of literature examining the effects of single (i.e., acute) bouts of exercise on cognitive function in the general population across the lifespan. This paradigm is important for identifying the ideal modality and intensity of an exercise stimulus for improving cognitive function for inclusion in a training study. This is because presumably, the acute effects of exercise on cognitive functioning will be additive during chronic exercise training much like the cumulative benefits of single bouts of aerobic exercise on cardiorespiratory fitness (Haskell, 1994). This section first highlights reviews and meta-analyses that have summarized the beneficial effects of acute bouts of exercise on cognition in the general population across the lifespan, and then reviews key exemplar studies involving successful paradigms for measuring cognition before and after acute bouts of exercise. Finally, this section describes a pilot study of

acute exercise on cognition in persons with MS that we recently completed to inform the development of the present study.

To date, the evidence describing the effects of acute exercise on cognitive function has been summarized in an initial comprehensive review (Tomporowski, 2003), and the overall effects have been quantified in two subsequent meta-analyses (Lambourne & Tomporowski, 2010; Chang et al., 2012). The initial review grouped studies involving the acute effects of exercise on cognition into three different categories: (a) studies examining cognitive performance following maximal exercise testing; (b) studies examining exercise-induced arousal on cognitive performance (i.e., studies that used the Yerkes-Dodson Law as a framework); and (c) studies examining the effects of relatively long, submaximal aerobic bouts of exercise on cognition (Tomporowksi, 2003). Based on the experimental design of the current study, this section only discusses the results from that third grouping. Briefly, a majority of the reviewed studies, mostly involving healthy college students as participants, did report significant improvements in cognition following acute bouts of aerobic exercise (i.e., ~73%). However, a small minority of the studies included in this classification did not report positive associations between acute aerobic exercise and cognitive function (i.e., ~13%). Nevertheless, that review summarized that exercise, when performed as treadmill exercise or cycle ergometry, exerted a selective, beneficial effect on cognition, when performed at a moderate intensity for fewer than 90 minutes (Tomporowski, 2003). The largest effects of acute aerobic exercise were for complex problem solving and executive functioning, in particular, with additional benefits on tasks involving speed of decision-making; that review then described that acute aerobic exercise did not seem to affect perceptual tasks (i.e., stimulus identification) (Tomporowski, 2003).

The overall effects of acute exercise on cognition have been quantitatively summarized by two recent meta-analyses (Lambourne & Tomporowski, 2010; Chang et al., 2012). The first meta-analysis examined 40 total studies yielding 235 total effects involving the acute effects of aerobic exercise on cognitive functioning in healthy adults (Lambourne & Tomporowski, 2010). That meta-analysis separately examined the effects of aerobic exercise on cognition both during and following exercise. Each study that was included in the meta-analysis involved repeated-measures, within-subjects designs.

Overall, when cognitive performance was measured *during* acute aerobic exercise, there were small, negative effects on cognition (i.e., $\Delta = -0.14$); those effects were stronger (i.e., more negative) for processing speed tasks. This suggests that processing speed decreases during acute aerobic exercise in healthy adults. One moderator of the acute exercise/cognition association was the time at which cognitive performance was assessed during exercise. There were mostly negative effects on cognition when measured during the first 20 minutes of aerobic exercise, whereas there were mostly positive effects on cognition when measured after at least 20 minutes of aerobic exercise (Lambourne & Tomporowski, 2010). This suggests that cognitive performance seems to worsen during the first twenty minutes of an aerobic exercise bout, but is seemingly enhanced after this point (i.e., rebound effect). An additional moderator included the modality of aerobic exercise, with more positive effects occurring for cycle ergometry and more negative effects for treadmill exercise (Lambourne & Tomporowski, 2010). This meta-analysis did not examine the negative effects of treadmill exercise on cognitive function based on walking or running exercise. Of note, since the publication of that meta-analysis, there is evidence that suggests that cognitive performance might not change during acute aerobic exercise in preadolescent children (Drollette et al., 2012).

On the other hand, when cognition was measured *following* acute bouts of aerobic exercise, there were overall positive effects on cognitive functioning that were small in magnitude (i.e., $\Delta = 0.20$). One moderator of the acute exercise/cognition association (when cognition was measured after exercise) was the cognitive domain that was examined. When measuring cognitive performance following acute aerobic exercise, there were larger effects on learning and memory and smaller effects on processing speed tasks. In general, the effects of acute exercise on cognition were larger following cycle ergometry, and smaller following treadmill exercise (Lambourne & Tomporowski, 2010).

One limitation of that meta-analysis was the overall small number of studies and effects that were included, based on the overall lack of evidence for acute aerobic exercise on cognition at the time of publication (Chang et al., 2012). To that end, a more recent meta-analysis provided an updated summary of the effects of acute exercise (including both aerobic and resistance exercise) on cognition in the general population, across the lifespan. That meta-analysis examined 79 studies that yielded 1034 effects—a volume of literature that was substantially larger than the number of studies and effects included in the previous meta-analysis (Chang et al., 2012). An important advantage of the more recent meta-analysis is that it included both healthy persons and persons with physical and cognitive limitations (Chang et al., 2012). Consistent with the previous meta-analysis, the more recent meta-analysis assessed the overall effects of acute exercise on cognition separately based on the timing of the measurement of cognitive performance. The authors quantified the effects of exercise on cognition when measured (a) during exercise; (b) immediately following exercise (i.e., within 1 minute of exercise completion); and (c) after a delay period of at least 1 minute following exercise.

Overall, there were small, positive effects of acute exercise on cognition (i.e., $g = 0.10$) regardless of the timing of cognitive measurement. When cognition was measured *during* exercise, there were small, positive effects of acute exercise on cognitive functioning ($g = 0.10$). Importantly, that meta-analysis identified the largest effects of acute exercise on tasks of executive function during exercise ($d = 0.26$), as well as larger effects when cognition was measured after at least 20 minutes of exercise (Chang et al., 2012). This suggests that during an acute bout of exercise, executive function is seemingly enhanced, in particular, after at least 20 minutes of exercise. This is not fully consistent with results from the previous meta-analysis (Lambourne & Tomporowski, 2010) describing largely negative effects on cognitive performance during acute exercise.

When cognition was measured *immediately after* exercise, there too were small, positive effects of acute exercise on cognitive functioning ($g = 0.11$). When cognition was measured immediately after exercise, the largest effects were on the domains of attention ($d = 0.42$), crystallized intelligence ($d = 0.27$), and executive function ($d = 0.19$). This suggests that immediately following acute exercise, those cognitive functions are seemingly enhanced. Importantly, intensity of exercise was identified as a significant moderator when cognition was measured immediately following exercise, such that there were larger effects for light ($d = 0.17$) and moderate ($d = 0.12$) intensity exercise, but there were no effects identified for hard, very hard, or maximal intensity exercise (Chang et al., 2012). This suggests that cognitive performance is enhanced immediately following light and moderate intensity exercise, in particular.

When cognition was measured after a delay following exercise, there were small, positive effects of acute exercise on cognitive functioning ($g = 0.10$). When cognition was measured after

a delay, the largest effects of acute exercise were for crystallized intelligence (d = 0.28) and executive functioning tasks (d = 0.17). This suggests that acute exercise seemingly benefits crystallized intelligence and executive functions after a delay period following an exercise bout. Exercise intensity was identified as a moderator when cognition was measured after a delay period, such that there were positive effects on cognition when exercise was performed at a light, moderate, hard, very hard, or maximal intensity (d > 0.20). Interestingly, there was an apparent dose-response effect, such that the largest effects of acute exercise on cognition following a delay period were for the most intense exercise stimuli, whereas the smallest effects were for exercise stimuli that were performed at a very light intensity (Chang et al., 2012).

That meta-analysis also examined the overall effects of acute exercise on cognition across different age groups. Acute exercise was significantly associated with cognition in children (d = .17), younger adults (d = .07), middle-aged adults (d = .18), and older adults (d = .18), independent of the timing of cognitive assessment (Chang et al., 2012). Importantly, when examining cognitive domain as a moderator in the overall sample, there were significant effects of acute exercise on executive function tasks including Stroop color-word interference (d = 0.25), digit-symbol substitution (d = 0.17), incompatible reaction time (d = 0.29), decision-making (d = 0.30), and verbal fluency (d = 0.31). There further were large effects identified for visual short-term memory (d = 0.23) and free-recall (d = 0.49) (Chang et al., 2012).

Individual studies have demonstrated that complex neurocognitive tests of executive control (i.e., modified flanker and Go/No-Go tasks) are particularly sensitive to acute aerobic exercise, as highlighted in a comprehensive review paper (e.g., Hillman et al., 2008). Neither meta-analysis on the overall effects of acute exercise on cognition included those tests as a moderator, when examining the effects of acute aerobic exercise on executive functioning

(Lambourne & Tomporowski, 2010; Chang et al., 2012). However, another recent, but smaller meta-analysis that evaluated the effects of acute exercise on executive function task performance did examine task complexity as a moderator variable (McMorris & Hale, 2012). For example, the authors hypothesized that increasing task complexity (i.e., complex central executive tasks, including inhibitory control based on modified-flanker task performance) would be more sensitive to the acute effects of aerobic exercise than simpler recall/basic attention tasks. The results from that meta-analysis indicated that indeed, there were larger effects on complex central executive tasks (g = 0.77) versus simpler recall/attention tests (g = 0.31). Further, on complex central executive tasks, the largest effects of acute aerobic exercise seemed to be for measures of speed, rather than measures of accuracy in studies involving adults (McMorris & Hale, 2012).

To that end, the above meta-analysis alluded to several highly successful studies of the effects of acute bouts of aerobic exercise on executive control using the modified flanker and Go/No-Go paradigms in the general population, across the lifespan. For example, one study used a within-subjects design to examine the effects of 20 minutes of treadmill exercise and quiet rest on inhibitory control using a modified flanker task in 20 preadolescent children (Hillman, Pontifex, Raine, Castelli, Hall, & Kramer, 2009). Children completed a 20-minute treadmill exercise condition (performed at 60% of maximal HR) and a 20-minute quiet rest condition on separate testing sessions. Participants undertook the flanker task approximately 25 minutes following each condition; the order of treadmill exercise and quiet rest conditions was counterbalanced across participants. Children demonstrated statistically significantly higher accuracy on incongruent trials of the modified flanker task following acute treadmill exercise relative to quiet rest; this effect was large in magnitude (η^2 = 0.21). There further were similar effects on interference control (i.e., the cost of interfering stimuli) on percent accuracy following

acute treadmill exercise (Hillman et al., 2009). There were no significant differences in RT based on congruency (i.e., incongruent vs. congruent trials) across sessions, though this null effect was expected, given that children are generally impulsive on such neurocognitive tests, whereby larger exercise effects are typically observed for accuracy outcomes over RT outcomes (e.g., Davidson, Amso, Anderson, & Diamond, 2006). That exemplar study supports the sensitivity of the modified flanker task in response to acute aerobic exercise.

Another study used a repeated-measures design to examine the effects of acute aerobic exercise and yoga on flanker task performance in 30 healthy female college students (Gothe et al., 2013). Participants underwent 20-minutes of treadmill exercise, performed at 60-70% of maximal HR, and 20-minutes of guided Hatha yoga on separate testing sessions; the order of conditions was counterbalanced across participants. Immediately following both exercise conditions, participants underwent a modified flanker task. Participants demonstrated statistically significantly higher response accuracy on incongruent trials following yoga exercise (i.e., 90.3%) compared with treadmill exercise (i.e., 83.4%); this effect was large in magnitude ($\eta^2 = .40$) (Gothe et al., 2013). There were no significant effects on RT between conditions ($\eta^2 = .02$). Although the results from that study deviate from the pattern of results that suggest that acute aerobic exercise affects measures of speed, rather than accuracy, on complex central executive tasks in adults (McMorris & Hale, 2012), this might indicate that different outcomes from the modified flanker task perhaps are sensitive to different modalities of acute exercise.

The Go/No-Go task has also been used as a measure of executive control (i.e., response inhibition) following acute aerobic exercise. For example, one study used a repeated-measures, within-subjects design to examine the effect of different intensities of cycling exercise on P300 amplitude using the Go/No-Go task in 12 healthy adults (age 22-33) (Kamijo et al., 2004). The

P300 is a neuroelectric component (i.e., event-related potential; ERP) that reflects the allocation of attentional resources in response to a given stimulus. All participants underwent a quiet rest control condition as well as cycle ergometer exercise conditions that were performed at high (i.e., maximal), medium (i.e., 12-14 on the Borg RPE scale), and low (i.e., 7-9 on the Borg RPE scale) intensities, respectively. The mean exercise duration for each session was approximately 18 minutes. Following each condition, participants immediately completed the Go/No-Go task while undergoing an ERP paradigm (i.e., electroencephalography measurement). For both Go and No-Go tasks, there were statistically significant differences in P300 amplitude based on exercise intensity ($p < .05$). P300 amplitude was largest following medium intensity exercise compared with high and low intensity exercise, respectively, and quiet rest (Kamijo et al., 2004). Results from this exemplar study suggest that the Go/No-Go task is a measure of executive control that might be sensitive to different intensities of acute aerobic exercise.

Importantly, we recently completed a pilot study (i.e., Project EXACT—Exercise and Cognitive Testing in MS) that examined the acute effects of different modalities of exercise on cognitive processing speed and executive control relative to a quiet rest control condition in 24 persons with mild MS disability (median EDSS = 3.0) using a completely within-subjects, repeated measures design (Sandroff et al., 2015a). We measured cognitive processing speed using the SDMT and executive control using a modified flanker task. Importantly, Project EXACT represents the first effort to examine the acute effects of exercise on cognition in MS. That study further represents the first effort to extend the application of the modified flanker task as a neurocognitive measure of executive control in a study of exercise and cognition in MS. All participants completed 5 testing sessions in our laboratory that were each separated by 7 days. Participants initially completed a baseline session that consisted of repeated cognitive testing to

minimize potential practice effects during sessions 2-5. Sessions 2-5 consisted of 20 minutes of quiet rest, moderate intensity treadmill walking exercise (i.e., 60% heart rate reserve (HRR)), moderate intensity cycle ergometer exercise (i.e., 60% HRR), and guided yoga that was adapted for persons with MS. The order of exercise and rest sessions was randomized and counterbalanced across participants such that the sample size of 24 allowed for one complete replication of the exercise conditions to minimize potential order effects of exercise conditions on cognitive processing speed and executive control. To examine the acute effects of each condition on cognition, we administered the SDMT and modified flanker task immediately before and after each condition. We further applied alternate forms of the SDMT and flanker task, respectively, across sessions to minimize potential carry-over effects on cognitive performance.

There were general pre-to-post improvements in RT (regardless of congruency), but not accuracy, on the modified flanker task for all three exercise modalities compared with quiet rest. Those effects were large in magnitude (all $\eta_p^2 > .24$). Of note, there were additional, selective improvements in RT based on congruency (i.e., pre-to-post reductions in the cost of interfering stimuli; interference control) on the modified flanker task for treadmill walking ($\eta_p^2 = .17$), but not cycle ergometry ($\eta_p^2 < .01$) or guided yoga ($\eta_p^2 < .03$), compared with quiet rest. There further were no effects identified for any of the exercise conditions relative to quiet rest for cognitive processing speed, based on SDMT scores, perhaps due to carry-over effects. The primary results from that pilot study seemingly support treadmill walking as the ideal modality of acute exercise for selectively improving executive control (i.e., interference control of RT) in persons with MS. However, the optimal *intensity* of treadmill walking exercise for selectively improving executive control in persons with MS is unknown.

THE PRESENT STUDY

Prior to developing a RCT on the effects of treadmill walking exercise on executive control in MS, it is necessary to examine the dose-dependent effects of varying intensities of walking exercise on this cognitive function in MS (i.e., the present study). Coupled with the results of our previous pilot trial (Project EXACT), such an endeavor would then optimize the exercise stimulus for inclusion in a well-designed clinical trial of exercise training and cognition in mild MS by identifying the ideal intensity of treadmill walking exercise for improving executive control in this population. The current study examined the effects of twenty-minute bouts of light, moderate, and vigorous intensity treadmill walking exercise compared with a quiet rest control condition on two aspects of executive control (i.e., interference control and response inhibition) in persons with MS, using a within-subjects, repeated-measures design.

Based on previous research using modified-flanker and Go/No-Go paradigms in healthy control subjects (Kamijo et al., 2004; Pontifex et al., 2013; Drollette et al., 2012), the primary hypothesis was that walking at a moderate intensity would exert the strongest acute effects on executive control compared with light and vigorous intensity walking, respectively. The secondary hypothesis was that those effects would be larger in cognitive tasks requiring greater levels of executive control (i.e., incongruent trials on the modified flanker task and No-Go task). This pilot study and our previous research provide important information regarding the optimal exercise stimulus for inclusion in a well-designed RCT for possibly improving executive control in MS. If successful, this line of research will ultimately provide clinicians and patients with better guidelines for using chronic exercise training as an approach for the management of cognitive impairment as a highly prevalent, poorly-managed, and life-altering symptom of MS.

Chapter 3—Methods

Participants

The procedure was approved by the University of Illinois at Urbana-Champaign Institutional Review Board, and all participants provided written informed consent. Prospective participants with MS were recruited from the local community using flyers, support group meetings, neurologists, and our database of previous MS participants. During the initial contact, the experimenter explained the general study protocol to prospective participants over telephone or e-mail. If the prospective participant expressed interest in the study, the experimenter undertook screening for inclusion criteria. The primary inclusion criteria involved: (a) being between 18-54 years of age; (b) a definite diagnosis of MS based on physician's confirmation of MS and its clinical course based on accepted criteria (Lubin & Reingold, 1996; McDonald et al., 2001; Poser et al., 1983); (c) being relapse-free over the past 30 days (i.e., relative neurologic stability); (d) being independently ambulatory (i.e., able to walk without an assistive device); (e) self-reported willingness and ability to walk on a motor-driven treadmill; (f) SDMT scores greater than 43 (i.e., no worse than 2 standard deviations below the normative score for healthy controls—this ensured that participants did not have severe cognitive impairment; Parmenter, Testa, Schretlen, Weinstock-Guttman, & Benedict, 2009); and (g) low risk for contraindications for maximal exercise testing based on a "no" response on all items of the Physical Activity Readiness Questionnaire (PAR-Q; Thomas, Reading, & Shephard, 1992) or a single "yes" response along with a physician's approval. The PAR-Q contains seven, yes/no items regarding contraindications for exercise testing (e.g., existing heart condition or chest pain at rest or during exercise) and is a standard screening inventory for stratifying risk for maximal exercise testing. Forty-nine prospective MS participants were contacted, with 33 remaining interested after

phone/e-mail contact; those individuals subsequently underwent screening. Of those 33 individuals, 3 did not qualify for the study based on having a recent relapse or reporting two "yes" responses on the PAR-Q. One additional participant was excluded based on a SDMT score of 39. Of those 29 participants who qualified based on inclusion criteria, 5 canceled their testing session citing lack of time. This resulted in a final sample size of 24 ambulatory participants with MS. The sample size allowed for one complete replication of the randomized, counterbalanced conditions to minimize potential order effects of exercise conditions on executive control. All participants were remunerated $100 following the completion of the study (i.e., $20 per session).

Primary Measures

Executive Control. This study measured executive control (e.g., inhibitory control) using a modified Eriksen flanker task (Eriksen & Eriksen, 1974) and a Go/No-Go task (Nosek & Banaji, 2000). There is evidence in healthy control subjects that both tests are highly sensitive to the acute effects of aerobic exercise (e.g., Hillman et al., 2009; Kamijo et al., 2004). Further, both tests have been used in NIH-funded trials of exercise on cognition (e.g., Chaddock-Heyman et al., 2013; Kamijo et al., 2012).

The modified flanker task has been included in the NIH toolbox for cognition as the primary measure of inhibitory control (i.e., interference control) and attention (Slotkin et al., 2012). This paradigm requires individuals to inhibit task-irrelevant information in order to correctly respond to a centrally presented target stimulus amid either congruent (<<<<<) or incongruent flanking stimuli (<<><<). Participants are required to press a left button on a keyboard (i.e., the 'z' key) if the target stimulus is pointing to the left and a right button on a keyboard (i.e., the 'm' key) if the target stimulus is pointing to the right, regardless of condition (i.e., congruent or incongruent). The stimuli consisted of 3 cm tall white arrows presented on a

black background with a jittered inter-trial interval (ITI) of 1100, 1300, or 1500 milliseconds (ms). Participants completed 1 block of 200 stimuli (100 congruent/100 incongruent, occurring with equal probability in a randomized order). Outcomes from the modified flanker task include mean percent accuracy and RT (ms) for congruent and incongruent trials, separately. Another outcome from the modified flanker task is interference control, which is calculated for percent accuracy as (percent accuracy on congruent trials – percent accuracy on incongruent trials) and for RT as (RT on incongruent trials – RT on congruent trials) to provide positive values for both measures. This further provides a measure of the cost of interfering stimuli on executive control. Total test time is approximately 5 minutes.

The Go/No-Go task is an additional measure of inhibitory control (i.e., response inhibition) (Nosek & Banaji, 2000). The "Go" task requires participants to respond via button-press on a keyboard (i.e., the 'm' key) to rare target stimuli (e.g., F, 20% probability) and withhold their response to frequent non-target stimuli (e.g., T, 80% probability), whereas the "No-Go" task requires participants to respond to frequent, non-target stimuli (e.g., T, 80% probability) and withhold their response to rare, target stimuli (e.g., F, 20% probability; Nosek & Banaji, 2000). The "No-Go" task, in particular, requires greater levels of inhibitory control to complete correctly. The stimuli consisted of 3 cm tall white letters (i.e., T or F) presented on a black background with a fixed duration of 150 ms and a jittered ITI of 1300, 1500, or 1700 ms. Participants completed 1 block of 125 stimuli for both "Go" and "No-Go" tasks. The primary outcome from the Go/No-Go task includes percent accuracy to rare target stimuli for both "Go" and "No-Go" tasks, though percent accuracy on the "No-Go" task is the outcome of interest for the current study (Kamijo et al., 2012). Total test time is approximately 10 minutes. Importantly, our previous research favors the use of repeated administration of computerized tests of

cognitive function before and after acute bouts of exercise over repeated administrations of paper-based neuropsychological tests (e.g., SDMT), based on an apparent carry-over effect (Sandroff et al., 2015a).

Cardiorespiratory Fitness. Cardiorespiratory fitness, operationally defined as peak oxygen consumption (VO_{2peak}), was measured using an incremental exercise test on an electronically-braked, computer-driven cycle ergometer (Lode BV, Groningen, The Netherlands) and a metabolic cart designed to collect and assess respiratory gases (TrueOne, ParvoMedics, Sandy, UT). This test was necessary for the precise prescription of exercise intensity in the subsequent acute sessions (i.e., measurement of peak heart rate (HR) and resting HR for calculating HR reserve). Participants undertook the incremental exercise test on a cycle ergometer as cycling overcomes safety issues such as foot drop and other signs of paresis that can make maximal exercise on a treadmill unsafe for persons with MS (White & Dressendorfer, 2004; Motl & Fernhall, 2012). Participants were initially fitted to the cycle ergometer, given standardized and tape-recorded descriptions of the test procedures, and allowed to ask questions. Participants were then outfitted for the collection of expired gases and rested for 1 minute on the cycle for measurement of resting HR. This was followed by a 3 minute warm-up at an initial work rate of 0 Watts (W). The work rate continuously increased at a rate of 15 $W \cdot min^{-1}$ until the participant volitionally terminated the test. This test protocol is a validated protocol for use in individuals with MS (Motl & Fernhall, 2012). Oxygen consumption (VO_2) and respiratory exchange ratio (RER) were measured every 20 seconds. HR (using a Polar heart rate monitor (Polar Electro Oy, Kempele, Finland)) and RPE were recorded every minute during the test. VO_{2peak} was defined as the highest recorded VO_2 value when two of three criteria are satisfied:

(1) RER ≥1.10; (2) HR_{peak} within 10 beats·min^{-1} of age-predicted maximum (i.e., ~1 SD); or (3) RPE_{peak} ≥17.

Cognitive Processing Speed. The oral version of the SDMT was included as a measure of cognitive processing speed (Smith, 1982; Benedict et al., 2006b). This measure was not used to document the acute effects of varying intensities of treadmill walking exercise on cognition. Rather, participants were screened for severe cognitive impairment using this neuropsychological test. Scores under 44 (i.e., severe cognitive impairment; Parmenter et al., 2009) resulted in exclusion from the study. The SDMT has been validated in persons with MS, and is widely recognized as the most sensitive measure of cognitive processing speed in this population (Benedict & Zivadinov, 2011). Briefly, participants were presented with a page showing symbols paired with single digit numbers in a key. The task was to voice correct numbers for unpaired symbols as rapidly as possible for 90 seconds. Responses were recorded by the examiner. The primary outcome measure was the number of correct responses provided in 90 seconds (i.e., raw score; Benedict & Walton, 2012). SDMT scores further were used for describing the baseline cognitive status of the sample.

Disability Status. All participants underwent a neurological exam by a Neurostatus-certified examiner who generated Expanded Disability Status Scale (EDSS; Kurtzke, 1983) scores for describing the disability status of the sample. Participants with EDSS scores within the range of 0-4.0 were included in the study.

Procedure

The overall flow of testing is presented in Figure 1. Participants completed 5 testing sessions at the same time of day, separated by 1 week, and were asked to abstain from exercising for 12 hours before testing sessions.

Baseline Session. All participants provided written informed consent followed by completion of the SDMT. SDMT scores under 44 (i.e., severe cognitive impairment; Parmenter et al., 2009) resulted in exclusion from the study. Participants then completed a short demographics questionnaire and undertook the executive control tests in a quiet, sound-dampened room. Prior to the initial administration of these tests, the experimenter read standardized instructions for successfully completing each test. Further, for each test, participants completed a practice trial consisting of 20 stimuli to ensure that they understood the test instructions and completed each test correctly. Following the practice trials, participants then completed the modified flanker and Go/No-Go tasks, respectively. Both cognitive tasks took approximately 15 minutes to complete. Next, a Neurostatus-certified assessor administered a brief neurological examination for generation of an EDSS score for describing the sample. Participants then undertook the incremental maximal exercise test on a cycle ergometer. This test provided a measure of cardiorespiratory fitness and oxygen consumption as a function of HR for subsequent and precise prescription of the exercise intensities for the remaining submaximal exercise sessions. Immediately following the exercise test, participants underwent a second administration of executive control measures. This repeated cognitive testing during the baseline session served to minimize possible practice effects during sessions 2-5.

Sessions 2-5. Those sessions occurred in a completely within-subjects design and the order of sessions was randomized and counterbalanced. Participants initially undertook 10 minutes of quiet rest, completed the modified flanker and Go/No-Go tasks while seated in a quiet, sound-dampened room in a comfortable chair in the laboratory, and then performed the assigned condition. Importantly, throughout the study, the modified flanker task was consistently administered prior to the Go/No-Go task. The control condition involved sitting quietly for 30

minutes in a comfortable chair; the three bouts of treadmill walking began with a 5 minute warm-up on the treadmill, then 20 minutes of walking at a speed and grade associated with either 30% (light), 50% (moderate), or 70% (vigorous) HRR (ACSM, 2013) and a 5 minute cool-down. The treadmill speed was initially selected based on ACSM equation based on energy expenditure (ACSM, 2013), and the actual intensity was monitored and documented by HR and RPE. Upon completion of the control or exercise bouts, participants again sat in a comfortable chair and completed the modified flanker and Go/No-Go tasks within 5 minutes following the condition (i.e., when HR returned near resting levels). All participants were remunerated following the completion of the 5th session.

Data Analysis

The data were initially examined for normality violations, outliers, and errors. The primary analytic model involved a 4 × 2 repeated-measures analysis of variance (ANOVA). This was performed on measures of executive control to examine the hypothesis of differential effects of varying intensities of treadmill walking exercise on measures of executive control compared with quiet rest. Separate 4 × 2 ANOVAs were performed on RT and accuracy measures from the modified flanker task for interference control, congruent trials, and incongruent trials, as well as on percent accuracy from the No-Go task. This was done to examine the hypothesis of larger acute exercise effects on cognitive tasks requiring greater levels of executive control. For all 4 × 2 ANOVAs, condition (light, moderate, vigorous, and rest) and time (pre- and post-) were included as within-subjects factors. If statistically significant, the overall interactions were decomposed with follow-up ANOVAs and *t*-tests. Effect sizes are expressed as partial eta-squared (η_p^2), with values of .01, .06, and .14 interpreted as small, moderate, and large, respectively (Cohen, 1988). Effect sizes for change over time per exercise condition relative to

quiet rest further are expressed as Cohen's *d* (i.e., change over time for individual exercise condition minus change over time for quiet rest, divided by pooled standard deviation), interpreted as small, moderate, and large based on criteria of 0.2, 0.5, and 0.8, respectively (Cohen, 1988).

Chapter 4—Results

Participant Characteristics

Demographic and clinical characteristics of the sample are presented in Table 1. Briefly, the mean age of the sample was 40.2 years, and the sample was primarily female (95.8%). Most participants reported at least a partial college education (i.e., 87.5%), and were employed (i.e., 83.3%). All participants had a relapsing-remitting clinical disease course; this was not an *a priori* inclusion criterion for study participation. The sample was characterized by a relatively mild MS disability status, based on a median EDSS score of 3.0 (range = 1.5-4.0) (e.g., Confavreux & Vukusic, 2006). Regarding baseline cognitive processing speed, the sample had a mean SDMT score of 63.1 (*SD* = 10.3). That value is 0.30 *SD*-units below the regression-based normative value (that controlled for age, sex, and education) for healthy controls (Parmenter et al., 2009) thereby indicating that our sample, on average, did not have slowed cognitive processing speed. However, five participants (i.e., 20.8%) did demonstrate impaired cognitive processing speed based on SDMT scores more than 1.5 *SD*-units below the regression-based normative value for healthy controls. All participants fulfilled at least 2 of the 3 criteria for determining VO_{2peak}, and the mean aerobic capacity of the sample was 23.5 ml/kg/min (*SD* = 5.5); this value is similar to other samples of persons with mild MS disability (e.g., Sandroff et al., 2015b).

Manipulation Check

Mean predicted 30% HRR value (i.e., light intensity) based on HR data from the incremental exercise test for the overall sample was 103.3 beats per minute (bpm; *SD* = 10.7). Mean actual peak HR for the light intensity condition was 104.9 bpm (*SD* = 10.0), and mean RPE for this condition was 9.7 (*SD* = 2.2) (i.e., between very light and fairly light perceived exertion). Mean predicted 50% HRR value (i.e., moderate intensity) based on HR data from the

incremental exercise test for the overall sample was 120.4 bpm (*SD* = 11.3). Mean actual peak HR for the moderate intensity condition was 121.2 bpm (*SD* = 11.7), and mean RPE for this condition was 12.5 (*SD* = 2.2) (i.e., somewhat hard perceived exertion). Finally, mean predicted 70% HRR value (i.e., vigorous intensity) based on HR data from the incremental exercise test was 137.3 bpm (*SD* = 12.8). Mean actual peak HR for the vigorous intensity condition was 137.0 bpm (*SD* = 14.5), and mean RPE for this condition was 15.2 (*SD* = 1.7) (i.e., hard perceived exertion). Collectively, this indicates that each intensity of treadmill walking exercise was performed within 1.5% of the prescribed %HRR, and that the 30%, 50%, and 70% HRR conditions were associated with light, moderate, and vigorous intensity exercise, respectively (ACSM, 2013).

Modified Flanker Task—RT

Descriptive data for measures of RT from the modified flanker task based on condition, time, and congruency are presented in Table 2 and the summaries of the three separate 4 × 2 ANOVAs on measures of RT are in Table 3. Values for RT on the modified flanker task further are consistent with those from our previous pilot study (Sandroff et al., 2015a).

Interference Control. The first 4 × 2 ANOVA indicated an overall large, statistically significant, condition × time interaction ($F(3,69) = 4.27$, $p = .01$, $\eta_p^2 = .16$) on interference control of RT. Light ($d = -0.63$), moderate ($d = -0.45$), and vigorous ($d = -0.63$) intensity treadmill walking exercise were associated with a greater reduction in the cost of interfering stimuli on RT compared with quiet rest (Figure 2). There were non-statistically significant main effects of condition ($F(3,69) = 0.43$, $p = .73$, $\eta_p^2 = .02$) and time ($F(1,23) = 1.25$, $p = .28$, $\eta_p^2 = .05$) on interference control of RT. To decompose the statistically significant overall 4 × 2 interaction on interference control of RT, a follow-up 3 × 2 repeated-measures ANOVA was

performed with condition (light, moderate, and vigorous) and time (pre- and post-) included as within-subjects factors. This follow-up ANOVA indicated a non-statistically significant condition × time interaction ($F(2,46) = 0.88$, $p = .42$, $\eta_p^2 = .04$) on interference control of RT such that there were similar pre-to-post reductions in the cost of interfering stimuli on RT for light, moderate, and vigorous intensity treadmill walking exercise.

Congruent Trials. The second 4 × 2 ANOVA indicated a non-statistically significant condition × time interaction ($F(3,69) = 1.78$, $p = .16$, $\eta_p^2 = .07$) on RT on congruent trials of the modified flanker task. There were not statistically significant pre-to-post reductions in RT overall for light ($d = -0.17$), moderate ($d = -0.26$), and vigorous ($d = -0.20$) intensity treadmill walking exercise relative to quiet rest. There further were non-statistically significant main effects of condition ($F(3,69) = 2.50$, $p = .07$, $\eta_p^2 = .10$) and time ($F(1,23) = 4.07$, $p = .06$, $\eta_p^2 = .15$) on RT on congruent trials of the modified flanker task.

Incongruent Trials. The third 4 × 2 ANOVA indicated a large, statistically significant condition × time interaction ($F(3,69) = 6.32$, $p < .01$, $\eta_p^2 = .22$) on RT on incongruent trials of the modified flanker task. There were substantial pre-to-post reductions in RT overall for light ($d = -0.43$), moderate ($d = -0.44$), and vigorous ($d = -0.48$) intensity treadmill walking exercise relative to quiet rest. There further was a statistically significant main effect of time ($F(1,23) = 4.54$, $p = .04$, $\eta_p^2 = .17$) on RT on incongruent trials of the modified flanker task, whereby there were pre-to-post reductions in RT, regardless of condition. There was a non-statistically significant main effect of condition ($F(3,69) = 2.09$, $p = .11$, $\eta_p^2 = .08$) on RT on incongruent trials of the modified flanker task. Collectively, this indicates that light, moderate, and vigorous intensity treadmill walking exercise had larger beneficial effects on RT on aspects of the

modified flanker task that required greater levels of executive control (i.e., incongruent trials relative to congruent trials).

Modified Flanker Task—Response Accuracy

Descriptive data for measures of response accuracy from the modified flanker task based on condition, time, and congruency are presented in Table 2 and the summaries of the three separate 4 × 2 ANOVAs on measures of response accuracy are in Table 4. Values for response accuracy on the modified flanker task further are consistent with those from our previous pilot study (Sandroff et al., 2015a).

Interference Control. The first 4 × 2 ANOVA indicated a non-statistically significant condition × time interaction ($F(3,69) = 1.03$, $p = .38$, $\eta_p^2 = .04$) on interference control of response accuracy. There were not statistically significant pre-to-post reductions in the cost of interfering stimuli on percent accuracy overall for light ($d = -0.40$), moderate ($d = -0.57$), and vigorous ($d = -0.12$) intensity treadmill walking exercise relative to quiet rest (Figure 3). There further were non-statistically significant main effects of condition ($F(3,69) = 0.22$, $p = .88$, $\eta_p^2 = .01$) and time ($F(1,23) = 1.42$, $p = .25$, $\eta_p^2 = .06$) on interference control of response accuracy.

Congruent Trials. The second 4 × 2 ANOVA indicated a non-statistically significant condition × time interaction ($F(3,69) = 1.20$, $p = .32$, $\eta_p^2 = .05$) on response accuracy on congruent trials of the modified flanker task. There were not statistically significant pre-to-post improvements in percent accuracy overall for light ($d = -0.32$), moderate ($d = -0.54$), and vigorous ($d = -0.45$) intensity treadmill walking exercise relative to quiet rest. There further were non-statistically significant main effects of condition ($F(3,69) = 1.01$, $p = .39$, $\eta_p^2 = .04$) and time ($F(1,23) = 0.20$, $p = .66$, $\eta_p^2 = .01$) on response accuracy on congruent trials of the modified flanker task.

Incongruent Trials. The third 4 × 2 ANOVA indicated a non-statistically significant condition × time interaction ($F(3,69) = 0.85$, $p = .47$, $\eta_p^2 = .04$) on response accuracy on incongruent trials of the modified flanker task. There were not statistically significant pre-to-post improvements in percent accuracy overall for light ($d = 0.03$), moderate ($d = -0.10$), and vigorous ($d = -0.28$) intensity treadmill walking exercise relative to quiet rest. There further were non-statistically significant main effects of condition ($F(3,69) = 0.43$, $p = .73$, $\eta_p^2 = .02$) and time ($F(1,23) = 0.85$, $p = .37$, $\eta_p^2 = .04$) on accuracy on incongruent trials of the modified flanker task. Collectively, this indicates that light, moderate, and vigorous intensity treadmill walking exercise seemingly did not have beneficial effects on percent accuracy on the modified flanker task relative to quiet rest that further did not differ based on level of executive control (i.e., congruency).

Go/No-Go Task—Response Accuracy

Descriptive data for measures of response accuracy from the Go/No-Go task based on condition and time are presented in Table 5. ANOVA was not performed on response accuracy for the Go task as this does not require high levels of executive control (i.e., response inhibition). There further was an apparent ceiling effect for the Go task, given that accuracies approached 100% for all four conditions (Table 5).

No-Go Task. The 4 × 2 ANOVA indicated a non-statistically significant condition × time interaction ($F(3,69) = 0.33$, $p = .81$, $\eta_p^2 = .01$) on percent accuracy on the No-Go task. There were not statistically significant pre-to-post improvements in percent accuracy overall for light ($d = 0.24$), moderate ($d = 0.24$), and vigorous ($d = 0.20$) intensity treadmill walking exercise relative to quiet rest (Figure 4). There further were non-statistically significant main effects of condition ($F(3,69) = 0.63$, $p = .60$, $\eta_p^2 = .03$) and time ($F(1,23) = 2.53$, $p = .13$, $\eta_p^2 = .10$) on

percent accuracy for the No-Go task. Collectively, this indicates that light, moderate, and vigorous intensity treadmill walking exercise seemingly did not have beneficial effects on response inhibition relative to quiet rest.

Chapter 5—Discussion

Results from previous RCTs of exercise training on cognition in persons with MS have been equivocal (Motl et al., 2011), perhaps due to incorrect exercise stimuli (i.e., modality and intensity of exercise). To that end, treadmill walking exercise has recently been suggested to be the modality of aerobic exercise that might exert the greatest beneficial effects on executive control in persons with MS (Sandroff et al., 2015a). The current study examined the dose-dependent effects of varying intensities of acute bouts of treadmill walking exercise on executive control outcomes in 24 persons with relapsing-remitting MS as the next step for identifying the appropriate exercise stimulus for possibly improving executive control in this population. The primary novel results of the present study were: (a) light, moderate, and vigorous intensity treadmill walking exercise significantly and similarly reduced the cost of interfering stimuli on RT on the modified flanker task relative to quiet rest; (b) there were no effects of exercise intensity relative to quiet rest on accuracy outcomes from the modified flanker task; and (c) there further were no effects of exercise intensity relative to quiet rest on the No-Go task. Collectively, this suggests that light, moderate, and vigorous intensity treadmill walking exercise might be appropriate exercise stimuli for inclusion in an exercise training intervention for improving speed-related aspects of executive control (i.e., RT). Those exercise stimuli might be particularly beneficial for improving performance on tasks that require greater levels of executive control (i.e., incongruent trials) in ambulatory persons with mild MS. The current results further suggest that those exercise stimuli might not be efficacious for improving accuracy-related aspects of executive control, namely interference control of percent accuracy or response inhibition.

The current results are exciting in that they represent the next step in identifying the optimal exercise stimulus for inclusion in an exercise training RCT for improving executive

control in persons with MS. Light, moderate, and vigorous intensity treadmill walking exercise were identified as having similarly beneficial effects on interference control of RT relative to quiet rest; those effects were large in magnitude. This has important implications for the development of such a RCT from an exercise prescription perspective. The present results support the development of a classical exercise training intervention that enhances cardiorespiratory fitness. This intervention would progressively include light, moderate, and vigorous intensity treadmill walking exercise as exercise stimuli for improving cardiorespiratory fitness *and* interference control of RT. In general, to enhance cardiorespiratory fitness, such well-established exercise training programs follow a three-stage model of exercise progression outlined by the ACSM (ACSM, 2013). The first stage of this model involves the initiation stage of aerobic exercise progression. This stage aims to prepare participants for more intense aerobic exercise (i.e., by accumulating small improvements in cardiorespiratory fitness) and develop an orthopedic tolerance for exercise stress (ACSM, 2013). For example, during the initiation stage, participants with poor cardiorespiratory fitness might exercise at light-to-moderate intensities (i.e., 30-50% HRR) for 15-30 minutes on 3-4 days per week for up to 4 weeks. Following this period, participants progress to the improvement stage. This stage provides a gradual increase in the overall aerobic exercise stimulus, whereby participants realize substantial improvements in cardiorespiratory fitness (ACSM, 2013). For example, during this stage, participants might exercise at moderate-to-vigorous intensities (i.e., 50-85% HRR) for 25-40 minutes on 3-5 days per week for up to 20 weeks. The final stage of exercise progression is the maintenance stage, which aims to maintain the levels of cardiorespiratory fitness that were developed during the improvement stage over the long-term (ACSM, 2013). This might involve exercising at vigorous intensity (i.e., 70-85% HRR) for 20-60 minutes on 3-5 days per week over time, depending on an

individual's exercise goals. The present results are particularly exciting in that they suggest that throughout such an exercise training intervention, persons with MS would presumably accumulate small acute improvements in interference control of RT at all three stages of exercise progression, as cardiorespiratory fitness improves and is maintained over time. Indeed, recent cross-sectional data seemingly suggest that better cardiorespiratory fitness is associated with shorter RT on the modified flanker task in persons with MS, and that improving fitness might have the potential for persons with mild MS to improve performance on this task to the level of a healthy control (Sandroff, Hillman, & Motl, *in press* (b)).

The current results further have important implications for the development of such a RCT from a compliance perspective. Given that all three intensities of treadmill walking exercise were associated with improved interference control of RT, persons with MS who are not accustomed to treadmill walking exercise or who have poor cardiorespiratory fitness might not have to engage in overly-intense exercise at the outset of exercise training in order to accumulate beneficial effects on executive control. Rather, the current results suggest that persons can begin such a program with bouts of light intensity exercise and still accumulate small acute improvements in interference control of RT. As comfortability with treadmill walking exercise and/or cardiorespiratory fitness improves, participants with MS can gradually engage in more intense bouts of exercise over time (i.e., exercise progression) while accumulating additional improvements in interference control of RT. To that end, this would presumably increase the likelihood of a participant complying with such an intervention, as the exercise progression (i.e., increases in intensity/duration) could be gradual while still optimally improving cognitive performance over time (ACSM, 2013). Finally, given that the largest acute exercise effects were on interference control of RT, such a RCT should consider examining the effects of treadmill

walking exercise training on brain structure and function in regions associated with interference control and cognitive processing speed (i.e., dorsolateral prefrontal cortex, thalamus) (e.g., Penner et al., 2003; Benedict et al., 2013) in persons with mild MS disability.

The current study replicates our previous work, which indicated that interference control of RT was improved following an acute bout of moderate intensity treadmill walking exercise relative to quiet rest in persons with MS (Sandroff et al., 2015a). The present results extend those previous results to include acute bouts of light and vigorous intensity treadmill walking exercise, in addition to moderate intensity treadmill walking exercise. Taken together, this indicates a generalized pre-to-post effect of varying treadmill walking exercise intensities on interference control of RT on the modified flanker task. The current study replicates the lack of pre-to-post improvements on percent accuracy on the modified flanker task following moderate intensity treadmill walking exercise relative to quiet rest in persons with mild MS disability (Sandroff et al., 2015a). The present results extend this lack of association to include light and vigorous intensity treadmill walking exercise, respectively. The lack of acute exercise effects on No-Go performance further is consistent with our previous work, as the primary outcome of the Go/No-Go task (i.e., a neurocognitive measure of response inhibition) is response accuracy. Collectively, this suggests that treadmill walking exercise might selectively improve speed-related aspects of interference control over accuracy-related aspects of this executive function and response inhibition. Such a pattern of results is similar to those from studies of acute exercise on cognition in adults of the general population, such that acute aerobic exercise has been found to improve speed-related aspects of executive control over accuracy-related aspects of executive control (McMorris & Hale, 2012). It is unlikely that the current pattern of results can be attributed to a speed-accuracy tradeoff (e.g., Salthouse, 1996), given that on the modified

flanker task, accuracy remained relatively unchanged following the exercise conditions, whereas RT decreased.

The primary hypothesis of the current study involved moderate intensity treadmill walking exercise exerting the greatest beneficial effects on executive control relative to quiet rest (i.e., inverted-U hypothesis/Yerkes-Dodson Law; Davey, 1973), based on previous acute exercise studies in the general population (e.g., Kamijo et al., 2004). The secondary hypothesis was that those effects would be largest in tasks requiring greater levels of executive control (i.e., incongruent trials/No-Go task). The present results were partially consistent with those hypotheses. Moderate intensity exercise did not exert the largest beneficial effects on executive control relative to quiet rest; rather, the acute effects of light, moderate, and vigorous intensity treadmill walking exercise on cognitive performance were not statistically different from one another. However, the effects were more pronounced for incongruent trials of the modified flanker task relative to congruent trials (i.e., interference control of RT), consistent with the secondary *a priori* hypothesis. In other words, the acute effects of treadmill walking exercise on executive control in persons with MS did not follow an inverted-U relationship (i.e., Yerkes-Dodson Law; Davey, 1973) that might have been driven by arousal (i.e., exercise intensity) (McMorris & Hale, 2012; Kamijo et al., 2004). This model posits that light intensity acute exercise (i.e., low arousal) results in sub-optimal cognitive performance, moderate intensity acute exercise (i.e., optimal arousal) results in maximal cognitive performance, and vigorous intensity acute exercise (i.e., high arousal) results in neural noise and sub-optimal cognitive performance (McMorris, Sproule, Turner, & Hale, 2011). Indeed, there is meta-analytic evidence supporting this inverted-U relationship of acute exercise intensities and cognitive performance in the general population (McMorris et al., 2011). Alternatively, the current results seemingly

indicate a generalized effect of treadmill walking exercise on cognitive performance in persons with mild MS disability, such that exercise intensity did not selectively influence cognitive performance on tasks of executive control.

We have previously speculated that treadmill walking exercise is essentially an inhibitory control task, and requires more attentional resources than other modalities of exercise (e.g., stationary cycling) (Sandroff et al., 2015a). The present results suggest that perhaps walking on a treadmill across multiple exercise intensities requires similar attentional resources for persons with mild MS disability. For example, it is plausible that light, moderate, and vigorous intensity treadmill walking all require participants to selectively attend to important central information in the visual domain for balance and coordination, and to selectively inhibit non-essential peripheral information (e.g., details of room setup) in order to maintain safety. We further speculate that with chronic treadmill walking exercise, such acute reductions in the cost of interfering stimuli on RT would be additive and cumulative over time (i.e., compensation). However, the potential mechanisms for how chronic treadmill walking exercise improves cognition in MS have not been directly tested. Future research should consider examining cognitive performance *during* acute bouts of aerobic exercise in persons with MS to test the hypothesis of whether treadmill walking exercise actually requires more attentional resources than other exercise modalities, and whether or not this varies based on exercise intensity.

Of note, the current examination represents a pilot study to delineate the optimal intensity of treadmill walking exercise for inclusion in an exercise training RCT for improving executive control in persons with mild MS disability. We have previously acknowledged that this approach does not aim to directly treat MS-related cognitive dysfunction overall (Sandroff et al., 2015a). The current sample did not demonstrate impaired cognitive processing speed based on SDMT

scores that were 0.30 *SD*-units below regression-based normative value for healthy controls (Parmenter et al., 2009). SDMT scores have often been considered a proxy of generalized cognitive dysfunction in MS (Benedict & Zivadinov, 2011). This sample of persons with MS was intentionally recruited in order to ensure that participants understood the directions of the cognitive and exercise protocols. As such, the current results provide proof-of-principle data supporting light, moderate, and vigorous intensity treadmill walking exercise for improving interference control of RT in persons with MS without slowed cognitive processing speed. Nevertheless, this highlights the importance of ultimately tailoring the exercise and cognitive stimuli for future exercise training RCTs for those with marked executive dysfunction (i.e., developing rehabilitation interventions for those with the most need). Further, it is unknown if such a RCT could result in more generalized effects on cognition, as there is a possibility that *chronic* treadmill walking exercise might improve cognitive processing speed, learning and memory, or other executive functions in persons with MS.

The current study involved a strong experimental design (i.e., within-subjects design, inclusion of a baseline session to minimize possible practice effects across conditions, randomization and counterbalancing of exercise intensities to minimize potential order effects), examination of multiple aspects of executive control (i.e., interference control and response inhibition) and continuation of a novel approach for delineating the optimal exercise stimulus (or stimuli) for improving executive control in persons with mild MS disability. However, there are several noteworthy limitations. As was the case with our previous research (Sandroff et al., 2015a), although randomizing and counterbalancing the experimental conditions across 24 persons with MS minimized the potential for order effects across sessions, it was not possible to entirely dismiss order effects as a potential explanation for the present results. This might have

been overcome by increasing the sample size and administering multiple randomized, counterbalanced orders of experimental conditions. As we previously observed (Sandroff et al., 2015a), there may have been possible ceiling effects for accuracy on the modified flanker and No-Go tasks. Participants demonstrated accuracies over 90% for each exercise intensity for the modified flanker task, and accuracies approaching 90% for each exercise intensity for the No-Go task. Those high accuracy levels are consistent with those from other acute exercise studies that have used the modified flanker paradigm (e.g., Pontifex & Hillman, 2007), but are higher than those from studies that have used the Go/No-Go paradigm (e.g., Niewenhuis, Yeung, & Cohen, 2004) in healthy adults of the general population. Perhaps the current MS sample implicitly prioritized accuracy over speed for both neurocognitive tasks, despite receiving explicit instructions to prioritize speed and accuracy equally (e.g., Sandroff, Benedict, & Motl, *in press* (a)). It is of note that there are no validity/reliability data on the modified flanker task as a neuropsychological measure of inhibitory control in MS; however, this task is highly reliable in older adults (Holtzer, Mahoney, & Verghese, 2014), and normative data are available for the general population in the NIH Toolbox scoring manual (Slotkin et al., 2012). The current sample only involved persons with relapsing-remitting MS, and the current results cannot be fully generalized to persons with progressive presentations of MS. The present results further are limited to those with relatively mild physical and cognitive MS disability who were able to walk on a motor-driven treadmill at vigorous intensity. This study involved persons with high levels of education (i.e., over 70% earned at least a college degree), and perhaps the results cannot be fully generalized to those with lower levels of education. Another limitation involves the lack of administration of a complete neuropsychological battery during the baseline session to better characterize the cognitive status of the sample. Finally, the current study did not control for

potential influences of age, sex, and disability status on the acute effects of varying intensities of treadmill walking exercise on executive control. The within-subjects, repeated-measures experimental design accounts for this, as participants serve as their own control, and variability among participants due to individual differences (i.e., age, sex, disability status) is completely removed from the error term (Stevens, 1996).

Chapter 6—Conclusions

There is evidence that treadmill walking exercise might be the modality of exercise that exerts the greatest beneficial effects on executive control in persons with mild MS disability. To that end, the current study is the first to examine the acute effects of varying intensities of treadmill walking exercise on multiple aspects of executive control in persons with mild MS disability. The present results support light, moderate, and vigorous intensity treadmill walking as exercise stimuli that might selectively benefit interference control of RT, but not accuracy-related aspects of interference control or response inhibition. This represents the next step in delineating the optimal exercise stimuli (i.e., modality and intensity) for inclusion in a subsequent longitudinal exercise training intervention for improving this cognitive function in persons with mild MS disability. Such results are especially exciting as including those three treadmill walking exercise intensities for improving cognitive performance in such an intervention is also advantageous for improving cardiorespiratory fitness and participant compliance. Ultimately, further testing is necessary to elucidate potential mechanisms as to how chronic treadmill walking exercise improves cognition in this population and to tailor the exercise stimuli amongst cognitively impaired MS samples.

Chapter 7—Tables and Figures

Table 1: Descriptive characteristics of 24 persons with MS.

Variable	**MS (N=24)**
Age (years)	40.2 (8.7)
Sex (n, % female)	23/24 (95.8%)
Education (n, %)	
High School	3/24 (12.5%)
Some College	4/24 (16.6%)
College/University Graduate	17/24 (70.8%)
Employment (n, % employed)	20/24 (83.3%)
Clinical Disease Course (n, % RRMS)	24/24 (100%)
Disease Duration (years)	8.1 (6.8)
EDSS (median, range)	3.0 (1.5-4.0)
SDMT (raw score)	63.1 (10.3)
VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)	23.5 (5.5)
Aerobic Exercise History (days/week)	3.0 (1.9)

Note: All data presented as mean (SD) unless otherwise noted; RRMS=Relapsing-remitting multiple sclerosis; EDSS=Expanded Disability Status Scale; SDMT=Symbol Digit Modalities Test; VO_{2peak}=Peak aerobic capacity.

Table 2: Measures of reaction time (RT) and response accuracy on a modified-flanker task based on condition, time, and congruency in 24 persons with MS.

	Light Intensity		Moderate Intensity		Vigorous Intensity		Quiet Rest	
Variable	*Pre-*	*Post-*	*Pre-*	*Post-*	*Pre-*	*Post-*	*Pre-*	*Post-*
Congruent-RT (ms)	412.0 (7.5)	406.9 (8.5)	410.9 (6.9)	402.5 (9.4)	407.3 (8.6)	400.2 (8.5)	412.2 (9.3)	414.0 (10.0)
Incongruent-RT (ms)	463.7 (10.1)	451.9 (10.2)	460.4 (8.7)	450.0 (10.8)	460.5 (9.5)	447.2 (9.9)	459.4 (10.4)	469.2 (11.3)
IC-RT (ms)	51.7 (5.2)	45.0 (4.1)	49.5 (4.8)	47.5 (3.9)	53.2 (4.9)	47.0 (4.6)	47.2 (4.4)	55.3 (4.2)
Congruent-Accuracy (%)	97.8 (0.8)	97.6 (1.1)	97.6 (0.9)	95.5 (2.8)	98.4 (0.3)	97.7 (0.8)	95.9 (2.5)	98.2 (0.7)
Incongruent-Accuracy (%)	92.6 (2.5)	94.3 (2.2)	92.9 (2.2)	93.0 (2.3)	94.7 (1.0)	93.4 (2.2)	92.7 (2.7)	94.0 (1.6)
IC-Accuracy (%)	5.2 (2.0)	3.4 (1.2)	4.8 (1.5)	2.5 (0.9)	3.7 (0.9)	4.3 (1.8)	3.2 (0.9)	4.3 (1.0)

Note: All data presented as mean (*SE*); RT=Reaction time; ms=milliseconds; IC=Interference Control

Table 3: Summary of 4 × 2 repeated-measures ANOVAs for the acute effects of light, moderate, and vigorous treadmill walking exercise and quiet rest on reaction time (RT) on a modified flanker task in 24 persons with MS.

	Congruent			Incongruent			Interference Control		
	F	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2
Condition × Time	1.78	.16	.07	6.32	<.01*	.22	4.27	.01*	.16
Condition	2.50	.07	.10	2.09	.11	.08	0.43	.73	.02
Time	4.07	.06	.15	4.54	.04*	.17	1.25	.28	.05

Table 4: Summary of 4 × 2 repeated-measures ANOVAs for the acute effects of light, moderate, and vigorous intensity treadmill walking exercise and quiet rest on percent accuracy on a modified flanker task in 24 persons with MS.

	Congruent			**Incongruent**			**Interference Control**		
	F	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2
Condition × Time	1.20	.32	.05	0.85	.47	.04	1.03	.38	.04
Condition	1.01	.39	.04	0.43	.73	.02	0.22	.88	.01
Time	0.20	.66	.01	0.85	.37	.04	1.42	.25	.06

Table 5: Measures of response accuracy on a Go/No-Go task based on condition and time in 24 persons with MS.

	Light Intensity		**Moderate Intensity**		**Vigorous Intensity**		**Quiet Rest**	
Variable	*Pre-*	*Post-*	*Pre-*	*Post-*	*Pre-*	*Post-*	*Pre-*	*Post-*
Go Accuracy (%)	100.0 (0.0)	99.8 (0.2)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)	99.5 (0.3)	100.0 (0.0)
No-Go Accuracy (%)	88.4 (2.5)	87.8 (2.2)	88.0 (1.8)	87.2 (2.4)	89.4 (1.9)	88.2 (1.9)	88.7 (2.0)	85.6 (2.9)

Note: All data presented as mean (*SE*);

Figure 1: Flow of Testing.

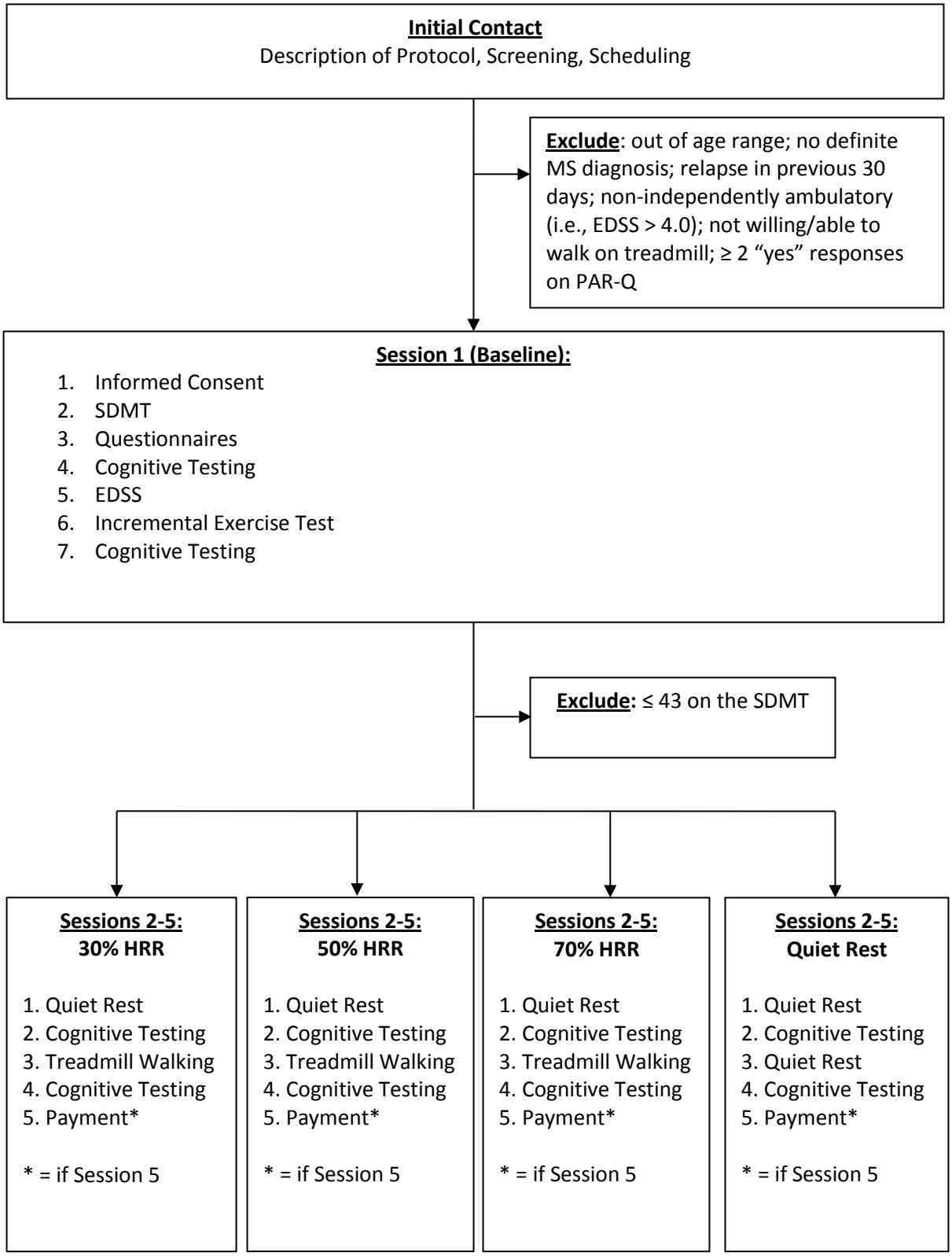


Figure 2: Acute effects of light, moderate, and vigorous intensity treadmill walking exercise and quiet rest on interference control of reaction time (RT; i.e., RT on incongruent trials minus RT on congruent trials) on a modified flanker task, along with standard error bars in 24 persons with MS.

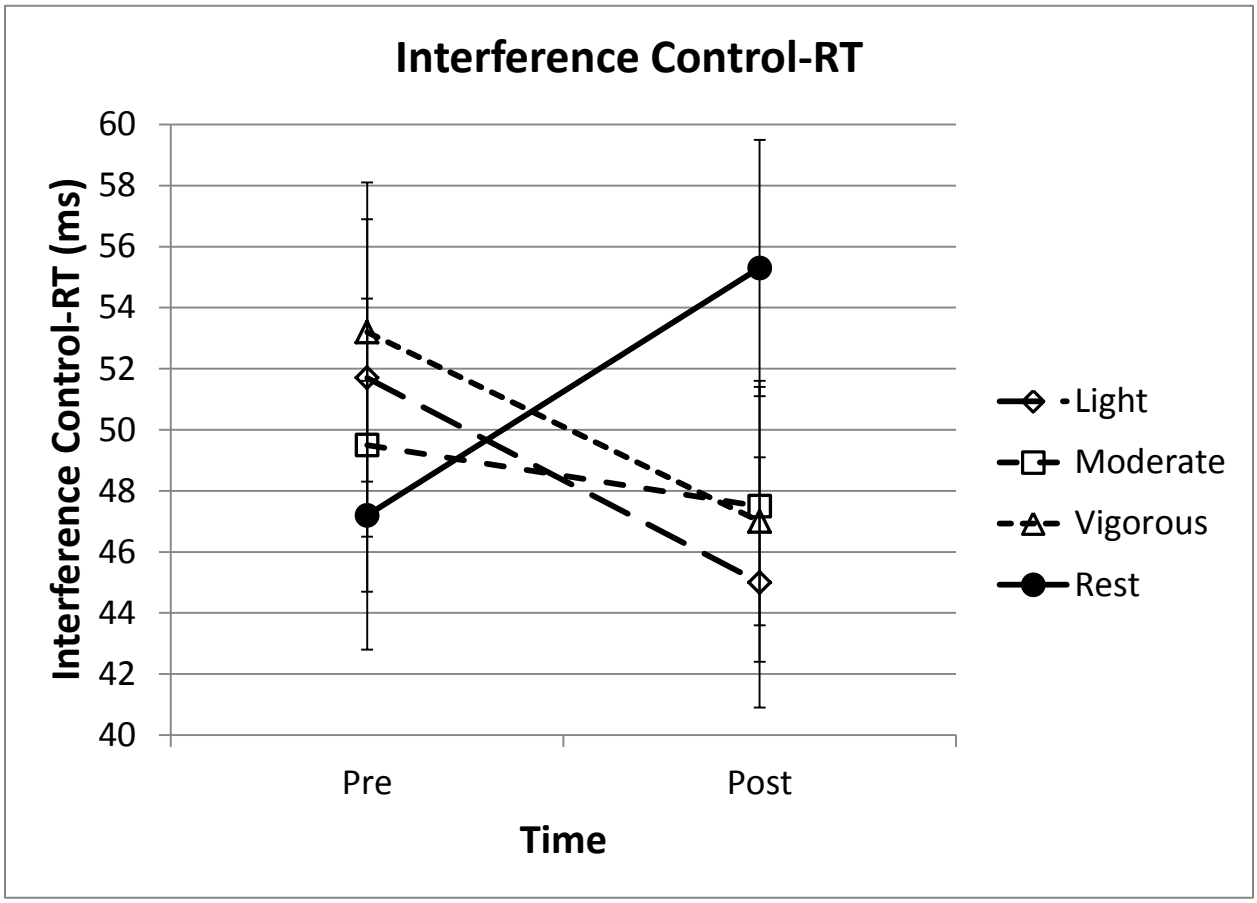


Figure 3: Acute effects of light, moderate, and vigorous intensity treadmill walking exercise and quiet rest on interference control of percent accuracy (i.e., accuracy on congruent trials minus accuracy on congruent trials) on a modified flanker task, along with standard error bars in 24 persons with MS.

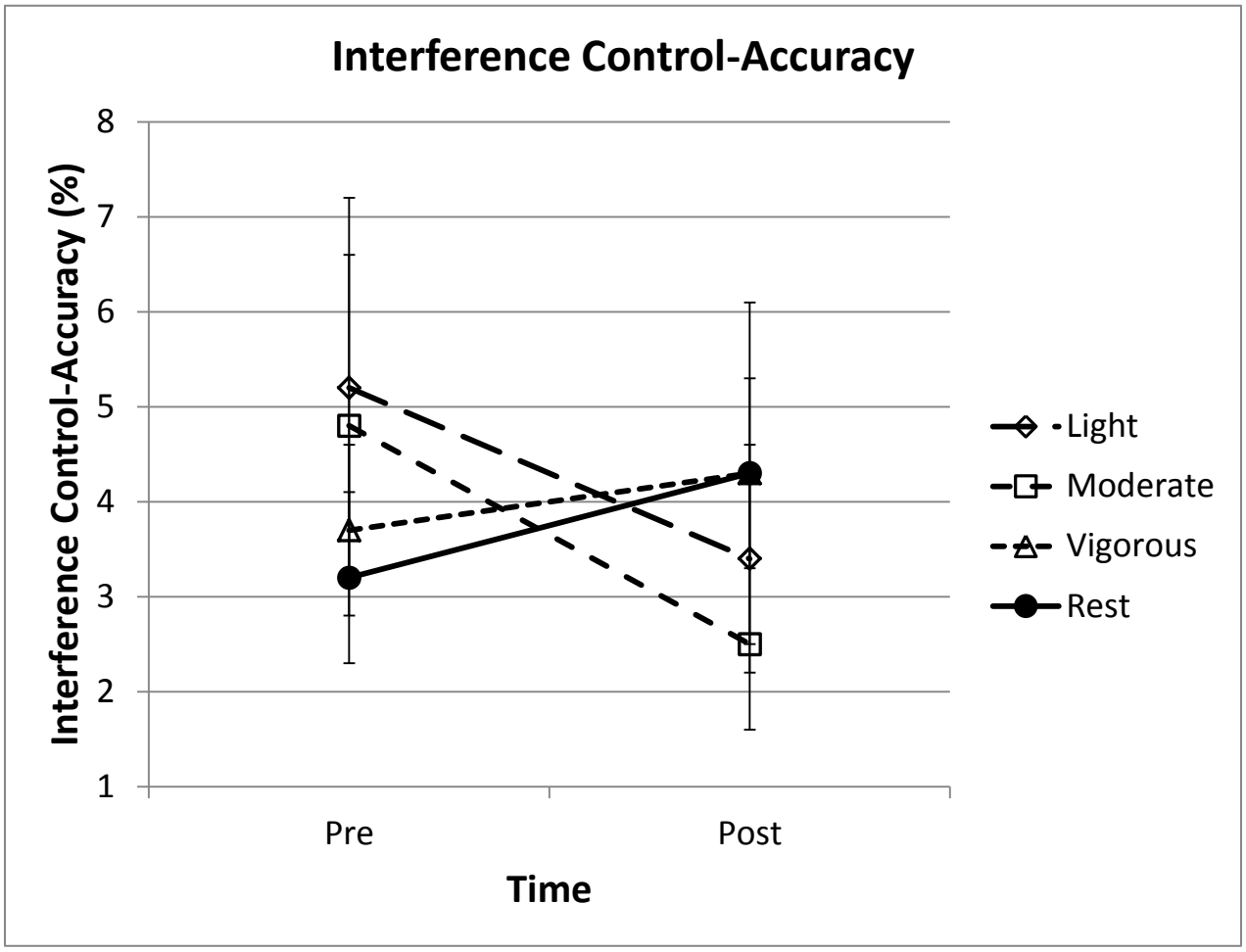
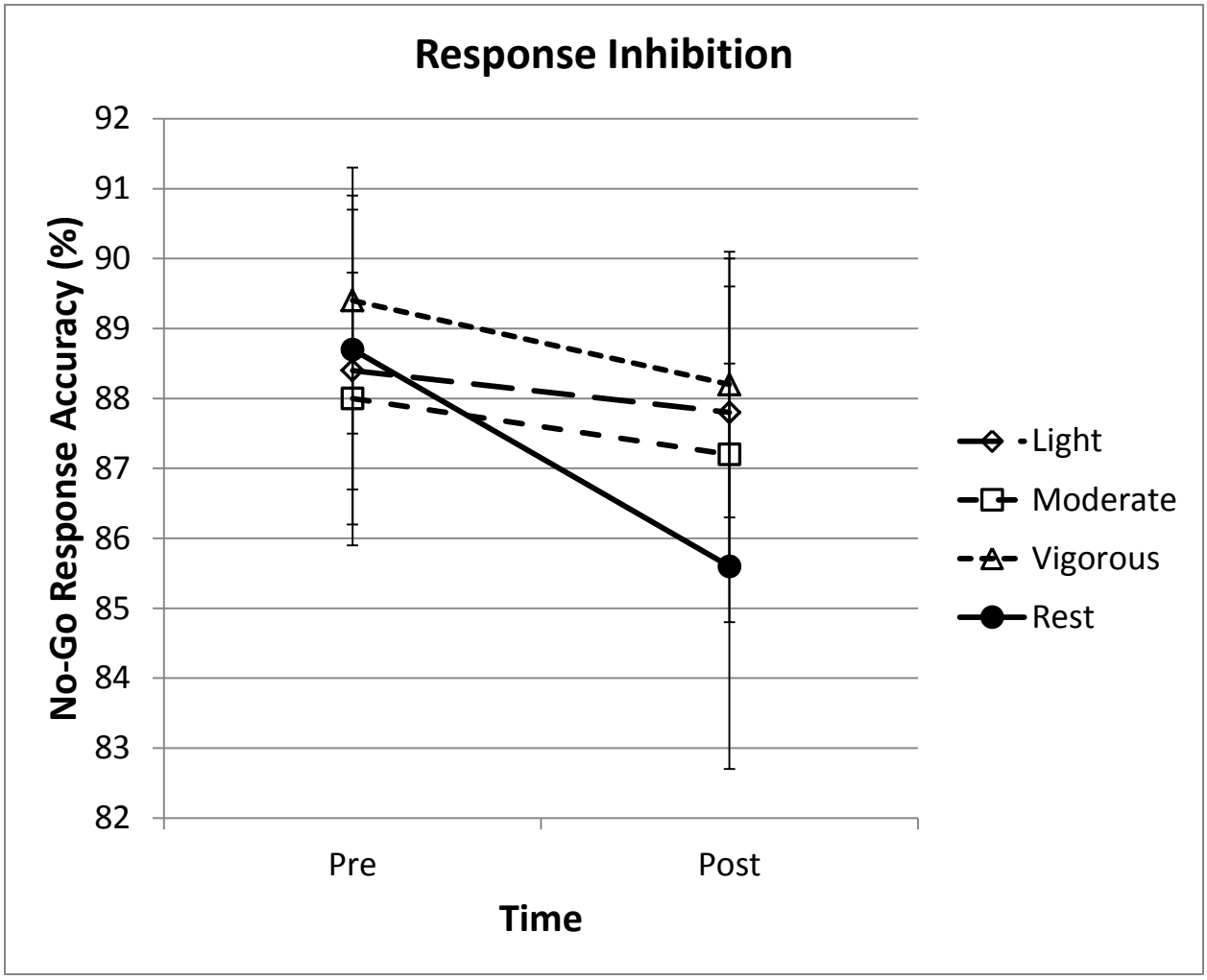


Figure 4: Acute effects of light, moderate, and vigorous intensity treadmill walking exercise and quiet rest on percent accuracy on a No-Go task (i.e., response inhibition), along with standard error bars in 24 persons with MS.



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