Multiple sclerosis (MS) is an autoimmune disease characterized by the production of widespread lesions in the brain and spinal cord. The disease is associated with a variety of disabling symptoms negatively affecting an individual’s functionality and quality of life. Cognitive impairment is evident in approximately half of those diagnosed with MS, yet no treatment to improve cognitive function in these individuals is available. A review of the literature in MS and cognitively similar populations suggests exercise may improve fitness and produce positive cognitive outcomes; however, several disease-associated symptoms, such as physical and motor limitations, pain, fatigue, and difficulty with temperature regulation are cited as barriers to exercising in this population. As such, fitness levels are typically lower in MS compared to the general population, which may further contribute to reduced functionality and cognitive impairment. Aquatic exercise is a kind of program that has successfully shown cognitive and fitness improvements in other populations, and may provide similar benefits and help to overcome common barriers in MS as well. The current study examined the effects of a very brief aquatic exercise intervention on cardiovascular fitness and cognitive function in individuals with MS. A total of 38 individuals participated in a one-week exercise intervention \( (n = 19) \) or control \( (n = 19) \) condition. Cognitive performance and fitness were assessed 24 hours pre-and-post intervention. In the interim, the exercise group participated in a daily exercise program, while the
control group was instructed to continue their typical routines. It was hypothesized that one week of aquatic exercise would produce positive changes in fitness and cognitive function. Fitness was proposed as a mediating factor for the relationship between group membership (i.e., exercise versus control) and post-intervention cognitive performance. Objective (heart rate) and subjective (rate of perceived exertion) measures of intensity, measured at several time-points during each exercise session, were proposed as key factors related to cognitive and fitness changes. As expected, fitness improved following the intervention in the exercise group, but not in controls. With the exception of learning and memory, cognitive performances improved for both groups on various measures. Reliable change index (RCI) calculations showed the percentage of reliable fitness and cognitive improvements was higher in the exercise group; however, RCI group comparisons showed that only fitness changes were significantly different. Contrary to expectations, the variables utilized in the meditational models were not significantly correlated, thus neither amount of fitness change nor total post-test fitness mediated the relationship between group membership and post-test cognitive function. Additionally, while change scores for fitness and cognitive tests did not correlate with subjective/objective intensity measurements, post-test fitness and cognitive performances did correlate with heart rate. Findings indicate those who participated in the exercise intervention showed statistically significant fitness benefits when compared to controls, though cognitive function did not significantly improve. Future work is necessary to determine whether this population benefits from a different type or dose of exercise to produce cognitive benefits.
THE EFFECTS OF A VERY BRIEF AQUATIC EXERCISE INTERVENTION ON FITNESS
AND COGNITIVE FUNCTION IN MULTIPLE SCLEROSIS

A dissertation submitted
to Kent State University in partial
fulfillment of the requirements for the
degree of Doctor of Philosophy

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TABLE OF CONTENTS

LIST OF FIGURES...........................................................................................................iv
LIST OF TABLES................................................................................................................v
ACKNOWLEDGEMENTS.....................................................................................................vi

CHAPTER

I  INTRODUCTION.............................................................................................................1
II  METHODS....................................................................................................................18
III  RESULTS....................................................................................................................34
IV  DISCUSSION...............................................................................................................42

REFERENCES....................................................................................................................58
LIST OF FIGURES

Figure 1. Cyclical Effects of Inactivity on Cognitive Function in MS……………………89
Figure 2. Fitness Change as a Mediator for the Relationship Between Exercise and
Cognitive Function…………………………………………………………………90
Figure 3. Partial Consort Table (n = 87) ……………………………………………………91
Figure 4a. Results of Mediational Bootstrapping: D-KEFS TMT4…………………………92
Figure 4b. Results of Mediational Bootstrapping: D-KEFS TMT-4, Post-test 2MST……93
Figure 5a. Results of Mediational Bootstrapping: DKEFS CWIT-3……………………94
Figure 5b. Results of Mediational Bootstrapping: D-KEFS CWIT-3, Post-test 2MST……95
Figure 6a. Results of Mediational Bootstrapping: Sorting Test-Confirmed Correct Sorts…96
Figure 6b. Results of Mediational Bootstrapping: Sorting Test-Confirmed Correct Sorts,
Post-Test 2MST……………………………………………………………………….97
Figure 7a. Results of Mediational Bootstrapping: COWAT……………………………98
Figure 7b. Results of Mediational Bootstrapping: COWAT, Post-test 2MST……………99
Figure 8a. Mean HR Measurements Across 7 Exercise Days……………………………100
Figure 8b. Mean RPE Measurements Across 7 Exercise Days……………………………101
Figure 9a. Mean HR Measurements Across All Intervals Throughout Exercise Week…..102
Figure 9b. Mean RPE Measurements Across All Intervals Throughout Exercise Week…103
Figure 10. Reliable Change Indices on Fitness and Cognitive Measures…………………104
LIST OF TABLES

Table 1. Studies Assessing Exercise and Cognitive Function in Multiple Sclerosis…...80
Table 2. Participant Demographics and Disease Characteristics (n= 38)…………………83
Table 2a. Possible Confounder Means at Pre- and Post-test by Groups…………………84
Table 3. Changes in Cardiovascular Fitness and Cognitive Measures Means by Groups...85
Table 4. Correlation Matrix Including 2MST Post-Test and Change Scores, Cognitive
Post-test Scores, HR, and RPE Measures…………………………………………………87
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CHAPTER I
INTRODUCTION

Multiple Sclerosis: Background

Multiple sclerosis (MS) is an inflammatory, degenerative autoimmune disease of the central nervous system (Weinshenker, 1994). It is the most common chronic disabling neurological disease in adults (Chwastiak et al., 2014), thought to affect more than 2.3 million adults worldwide (National Multiple Sclerosis Society, 2015), with an estimated annual treatment cost of over $50,000 per patient (Adelman, Rane, & Villa, 2013). The disease is characterized by the production of widespread lesions in the brain and spinal cord, affecting the neurons’ myelin sheath and thus inhibiting axonal transmission (Chiaravalloti & DeLuca, 2008).

The majority of individuals with MS present with subacute relapses involving the exacerbation of a variety of symptoms, followed by either complete or partial remission, depending on diagnosed subtype. Four basic disease subtypes have been defined on the basis of progression rate: relapsing-remitting, secondary-progressive, progressive-relapsing, and primary-progressive (Kaufman, 2003). Relapsing-remitting MS is characterized by periods of relapses with full recovery between exacerbations (Chiaravalloti & DeLuca, 2008). Approximately 80% of individuals with this diagnosis later develop secondary-progressive MS, characterized by gradually worsening symptoms with or without minor relapses. Progressive-relapsing MS involves progressive decline following disease onset with acute symptom relapse. Finally,
primary-progressive MS involves a continuous and gradual worsening of symptoms with no distinct remission (Kaufman, 2003). Relapses are considered clinically definite when neurological dysfunction becomes separated in space and time, and magnetic resonance imaging (MRI) findings of multifocal lesions are used to support clinical impressions (Noseworthy, Lucchinetti, Rodriguez, & Weinshenker, 2000).

Prognosis is variable in MS, though frequent relapses in the first two years are predictive of a more severe clinical course (Noseworthy et al., 2000). The early onset (typically between ages 20-50) and long duration of the disease result in significant individual, family, and societal costs (Grima et al., 2000). Although the cause of MS is currently unknown, interplay between immunological, viral, and genetic factors has been suggested (Rumrill, Kaleta, & Battersby, 1996). Symptoms associated with MS include impaired autonomic functioning, motor symptoms such as gait imbalance, muscle spasms, spasticity, weakness and numbness, loss of bladder/bowel control, sexual dysfunction, fatigue, pain, and depression (Mohr & Cox, 2001; Pierson & Griffith, 2006). One serious and highly prevalent symptom of MS is cognitive impairment (Amato, Ponziani, Siracusa, & Sorbi, 2001; Lovera & Kovner, 2012; Rao, Leo, Bernardin, & Unverzagt, 1991).

**Cognitive Impairment in MS**

Cognitive impairment occurs in approximately half of those diagnosed with MS (Benedict et al., 2006), and is apparent early in the disease, with worsening severity coinciding with disease duration (Brissart et al., 2013). Though the affected cognitive functions or domains may vary depending on the subtype of MS (Brissart et al., 2013), cognitive impairment is
typically evident in information processing speed, executive functioning, attention, working memory, learning, and long-term memory (Chiaravalloti & DeLuca, 2008; Simioni, Ruffieux, Bruggimann, Annoni, & Schluep, 2007). Cognitive impairment is associated with lower functional status (Amato et al., 2013), high caregiver burden (Figved, Myhr, Larsen, & Aarsland, 2007), lower rates of employment, social and vocational activities, and reduced instrumental activities of daily living (Chiaravalloti & DeLuca, 2008; Crayton & Rossman, 2006) in this population. Given that reduced cognitive function is so frequent and pervasive in this disease, understanding causal factors is important.

Many contributory mechanisms have been implicated in MS-related cognitive impairment, including major neuropathological substrates (e.g., lesion formation, demyelination, brain atrophy, etc.; Benedict & Zivadinov, 2011; Calabrese et al., 2009; DeLuca, Yates, Beale, & Morrow, 2015; Filippi et al., 2000, 2010; Grassiot, Desgranges, Eustache, & Defer, 2009; Hoffmann, Tittgemeyer, & von Cramon, 2007; Penner, Opwis, & Kappos, 2007; Rahn, Slusher, & Kaplin, 2012; Rovaris et al., 1998; Sahraian & Etesam, 2014; Shiee et al., 2012) and disease-associated symptoms, such as depression, fatigue, sleep impairment, and pain (Chiaravalloti & DeLuca, 2008; Pierson & Griffith, 2006; Sahraian & Etesam, 2014).

In addition, research suggests that lack of physical activity may also exacerbate cognitive impairment (Etgen et al., 2010) and other symptoms that occur in MS (Mostert & Kesselring, 2002; Vanner, Block, Christodoulou, Horowitz, & Krupp, 2008). Specifically, reduced physical activity may contribute to a decline in functionality and greater disability, a process referred to as “deconditioning” (Mostert & Kesselring, 2002), which in turn may exacerbate cognitive and other symptoms (see Figure 1). Indeed, levels of physical activity in those with MS are
reportedly lower than in the general population (Stuifbergen, 1997), further elevating risk for cognitive impairment in these individuals. In light of the extensive impact of cognitive impairment on the life of an individual with MS (Chiaravalloti & DeLuca, 2008; Crayton & Rossman, 2006), treatment and management are of utmost importance.

**Managing Cognitive Impairment in MS**

Although there is currently no cure for MS, some treatments are available, typically targeted at reducing the frequency and severity of relapses and facilitating symptom recovery (Noseworthy et al., 2000). Specifically, pharmacologic treatments with immunomodulatory properties, referred to as “disease modifying drugs,” have been developed and used extensively in the last two decades (Mendes & Sá, 2011). Pharmacologic treatments minimize many symptoms of MS; however, no medications have been approved for treatment of MS-related cognitive impairment (Beier, Bombardier, Hartoonian, Motl, & Kraft, 2014; Crayton & Rossman, 2006). In addition, existing treatments raise concerns related to route of medication administration, side effects, and safety, and adherence rates are typically low (Glanz et al., 2014).

Research suggests combination drug-based and non-drug-based, more modifiable treatment approaches, are most successful at reducing symptoms (Crayton & Rossman, 2006; Döring, Pfueller, Paul, & Dörr, 2012). One non-drug-based approach that has been explored specifically for cognitive impairment in those with MS is cognitive rehabilitation. However, the few rehabilitation studies that have been conducted have had significant methodological difficulties (as reviewed by O’Brien, Chiaravalloti, Goverover, & DeLuca, 2008) and clinically meaningful outcomes have not been shown in cognitive domains other than learning/memory
(Rosti-Otajärvi & Hämäläinen, 2014), just one of the many cognitive domains affected in MS. In addition, cognitive rehabilitation typically involves the application of compensatory strategies rather than deficit prevention or reversal (Bagert, Camplair, & Bourdette, 2002), which may be more imperative given the degenerative course of MS. More effective methods for managing cognitive impairment in MS are needed. Exercise represents one promising, modifiable and cost-effective tool for improving cognitive function in individuals with MS (Döring et al., 2012).

**Exercise for Improving Cognitive Function in MS**

A review of the exercise literature in MS suggests that both aerobic and resistance training are associated with several benefits in this population, such as reduced risk of relapse (Pilutti, Platta, Motl, & Latimer-Cheung, 2014), improvement of several associated symptoms and quality of life, and greater functional and fitness abilities (Bjarnadottir, Konradsdottir, Reynisdottir, & Olafsson, 2007; Dalgas et al., 2009; Döring et al., 2012; Gallien et al., 2007; Latimer-Cheung et al., 2013; Motl et al., 2005; Newman et al., 2007; Petajan et al., 1996; Pilutti, 2012; Romberg, Virtanen, & Ruutiainen, 2005; Sá, 2014; Taylor, Dodd, Prasad, & Denisenko, 2006; White & Dressendorfer, 2004). Cross-sectional examinations of physical activity, which includes exercise, have also shown positive associations with cognitive function in MS (Motl, Gappmaier, Nelson, & Benedict, 2011; Sandroff & Motl, 2012), and the outcomes of existing studies support the use of exercise as a tool for improving cognitive function in these individuals (Motl, Sandroff, & Benedict, 2011; Sá, 2014).

**Studies assessing exercise and cognitive function in MS.** Observational studies have examined the association between physical activity (including exercise) and cognitive function in individuals with MS, and have found that higher levels of objectively measured physical activity
are associated with better information processing speed (Motl et al. 2011a; Sandroff & Motl, 2012). In addition, nine intervention studies to date have examined the effects of physical activity/exercise on cognitive function specifically in MS (Beier et al., 2014; Briken et al., 2013; Leavitt et al., 2014; Oken et al., 2004; Pilutti, 2012; Romberg et al., 2005; Sandroff et al., 2014; Sandroff, Hillman, Benedict, & Motl, 2015; Swank, Thompson, & Medley, 2013), each with unique approaches and limitations (see Table 1). Briefly, intervention durations have ranged from acute assessments (i.e., a single 20-minute bout of exercise) to six months, and have consisted of different modalities, including yoga, aerobic training, resistance training, and combination exercise programs (i.e., aerobic and resistance training), as well as non-specific behavioral approaches (e.g., motivational coaching to promote any kind of physical activity). Following these interventions, improvements have been noted in various cognitive domains including executive functioning, inhibitory control, learning, memory, and attention. In general, successful interventions have been of moderate-to-high intensity and have occurred at least twice per week (Briken et al., 2013; Leavitt et al., 2014). Two of these intervention studies measured cognitive function following behavioral interventions that “promoted changes in exercise” rather than incorporating a standardized exercise prescription. Despite being limited by a lack of standardization, these behavioral intervention studies found a link between fitness changes and improved cognitive function (Beier et al., 2014; Sandroff et al., 2014). Three of these intervention studies failed to find cognitive benefit following exercise training in MS (Oken et al., 2004; Romberg et al., 2005; Swank et al., 2013). However, these outcomes may be attributed to the studies’ methodological restrictions, such as poor adherence rates, low frequency of exercise, lack of exercise standardization, and failing to assess fitness as an objective measure of exercise-
induced changes. Studies that address limitations of prior work such as these are necessary. For example, future work should consider assessing fitness both before and after an exercise intervention to help pinpoint causal factors for changes (or lack thereof) in cognitive function.

**The importance of fitness.** Based on work in MS and other populations, it appears that fitness is an important variable to consider when determining exercise intervention outcomes, as this represents a quantifiable result of exercise effectiveness on an individual basis (Beier et al., 2014). Given that fitness is based on an objective physiological measurement (Barnes, Yaffe, Satariano, & Tager, 2003), measuring fitness changes provides data reflecting exercise effectiveness. Similarly, failing to measure fitness changes following an exercise intervention, particularly in the event that an intervention that does not result in cognitive improvement, may lead to incorrect conclusions that exercise does not yield positive cognitive effects. Indeed, a comparison between MS studies that detected cognitive changes versus less fruitful interventions (see Table 1) suggests that measuring fitness may be an important step in evaluating the effects of exercise on cognitive function. Specifically, studies that detected significant fitness changes (generally cardiovascular fitness) tended to find concurrent positive cognitive effects, suggesting the inclusion of fitness assessment is an important consideration when designing exercise intervention studies aiming to improve cognitive symptoms in MS.

**Mechanisms for Cognitive Improvement through Exercise in MS**

**Proposed mechanisms.** It has been well established that exercise improves cognitive function in several populations (Chang, Labban, Gapin, & Etnier, 2012; Colcombe & Kramer, 2003; Heyn, Abreu, & Ottenbacher, 2004; Quaney et al., 2009; Sibley & Etnier, 2003). While
aerobic exercise has been consistently recommended for many positive cognitive effects (Erickson & Kramer, 2009; Hillman, Erickson, & Kramer, 2008; Smith et al., 2010), some studies have suggested that a combination of aerobic and resistance training produces the greatest effects on cognitive function (reviewed by Colcombe & Kramer, 2003). It has been posited that additional strength training provides greater physical resources to facilitate tolerability of aerobic training; however, strength training has also independently been associated with higher production of important growth factors associated with brain health (Schmitz, Ahmed, & Yee, 2002) and improved executive functioning performance in other populations (Cassilhas et al., 2007; Liu-Ambrose et al., 2010), suggesting this type of training may better enable cognitive enhancement. Certainly, both types of exercise may initiate several mechanisms that can contribute to cognitive improvement.

Although no one specific cause for cognitive improvement through exercise has been elucidated, several mechanisms have been proposed. In MS, alleviation of other disease-related symptoms, such as pain, depression, and fatigue through exercise may indirectly reduce cognitive impairment (Chang et al., 2012). Additionally, it is hypothesized that neurobiological responses to exercise, such as the formation of new neurons and blood vessels, enhanced production of growth factors (Cotman, Berchtold, & Christie, 2007; Eggermont, Swaab, Luiten, & Scherder, 2006; Vaynman & Gomez-Pinilla, 2005), higher brain volume (Colcombe et al., 2006; Erickson et al., 2011), and reduced inflammation (Cotman et al., 2007) are largely responsible for improvements in cognitive function (Chang et al., 2012).

Fitness change: a key mechanism. As reviewed thus far, many theories have been proposed regarding underlying mechanisms for cognitive changes following exercise. However,
research strongly suggests that exercise-induced changes in fitness, which is evidenced through cardiovascular fitness, muscle strength, body composition, or flexibility (Caspersen, Powell, & Christenson, 1985), may be at least partially responsible for changes in cognitive function (Barnes et al., 2003; Colcombe & Kramer, 2003; Sattler, Erickson, Toro, & Schroder, 2011). In particular, cardiovascular fitness (sometimes also referred to as aerobic or cardiorespiratory fitness) appears to be consistently implicated in the process of exercise-induced cognitive changes in studies with various populations (as reviewed by Aberg et al., 2009, Colcombe & Kramer, 2003, and Colcombe et al., 2004). Studies of this nature are generally based on the “cardiovascular fitness hypothesis,” which states that cardiovascular fitness explains the relationship between exercise and improved cognitive function (North, McCullagh, & Tran, 1990). Consistent with this theory, one meta-analysis of exercise intervention studies in older adults found that improved cardiovascular fitness was responsible for improving cognitive scores, particularly in executive functioning processes, by approximately 0.5 standard deviations regardless of the type of exercise or participant characteristics (Colcombe & Kramer, 2003). Such work suggests that cardiovascular fitness may be a key factor underlying improvement in cognitive function following an exercise intervention.

**Fitness, Exercise, and Cognitive Function in MS**

Though less common than studies in aging populations, research regarding exercise, fitness, and cognitive function in MS is encouraging. Observational studies in this population have positively correlated cardiovascular fitness with better performance on tasks of information processing speed and working memory (Prakash et al., 2007; Sandroff & Motl, 2012), as well as
gray matter and white matter structural integrity (Prakash, Snook, Motl, & Kramer, 2010) and
greater functional recruitment of task-related brain regions (Prakash et al., 2007). These findings
are quite important, as reduced gray and white matter volume have consistently been related to
cognitive impairment in MS (Bagert et al., 2002; Benedict et al., 2004; Filippi et al., 2010; Lanz,
Hahn, & Hildebrandt, 2007; Morgen et al., 2006; Zivadinov et al., 2001). Authors of these
studies suggested that improvements in fitness may reverse physiological deconditioning related
to reduced cognitive function. Certainly, fitness may be a key mechanism underlying the
relationship between exercise and changes in cognitive function (Barnes et al., 2003; see Figure 2).

Experimental studies that assess fitness changes in MS are promising as well: exercise
interventions have resulted in improved fitness variables, including cardiovascular fitness
(Briken et al., 2013; Mostert & Kesselring, 2002), muscle strength (Sá, 2014), walking
endurance (Van den Berg et al., 2006), and anaerobic threshold (Bjarndottir et al., 2007) in this
population. Based on these findings, it has been suggested that 30 to 60 minutes of moderate-
intensity aerobic exercise performed at least two to three times per week improves fitness in
those diagnosed with MS (Latimer-Cheung et al., 2014). Individuals in this population have been
shown to make cardiovascular fitness gains in as little as four weeks (Mostert & Kesselring,
2002), suggesting that interventions may not need to be of long duration to produce benefits.

To date, three exercise intervention studies specifically assessing cognitive function in
MS have incorporated fitness measures (see Table 1). Each of these studies also directly assessed
the relationship between improvements in various fitness variables and cognitive function (Beier
et al., 2014; Briken et al., 2013; Sandroff et al., 2014) and determined that changes in executive
functioning, attention, learning and memory, and information processing speed were related to fitness changes. However, only one of these studies was based on a controlled, standardized exercise intervention (Briken et al., 2013); the remaining two (Beier et al., 2014; Sandroff et al., 2014) involved only health promotion programs in which individuals were encouraged to exercise on their own accord. These studies are encouraging, but are methodologically limited due to a lack of standardization and experimental control. Thus, studies with more rigorous control strategies are required.

**How Might Fitness Improve Cognitive Function in MS?**

Several theories exist regarding the effects of improved fitness on cognitive function. It has been posited that gains in cardiovascular fitness achieved through physical activity are associated with many of the same processes implicated in the cognitive function/exercise literature across many populations, such as changes in cerebral structure, cerebral blood flow, and production of neurotrophic factors (Brown et al., 2010; Colcombe et al., 2003; Endres et al., 2003; Vaynman & Gomez-Pinilla, 2005; Zheng et al., 2005). It is conceivable that improving fitness may actually facilitate each of these neurobiological processes. Animal models have shown that improving fitness elicits a cascade of favorable neurobiological processes, including improved cerebral structural integrity (Motl et al., 2005), higher brain volume (Colcombe et al., 2006), improved cerebral blood flow (Swain et al., 2003), greater production of neurotrophic factors that are responsible for neurogenesis and neuron survival in the brain (Churchill et al., 2002; Neeper, Gomezpinilla, Choi, & Cotman, 1995; van Praag, Christie, Sejnowski, & Gage, 1999), and greater overall brain activation (Colcombe & Kramer, 2003; Colcombe et al., 2004).
Human research models, including two studies with individuals diagnosed with MS (Bansi, Bloch, Gamper, & Kesselring, 2012; Gold et al., 2003) have associated a variety of these processes with higher fitness levels and improved cognitive function as well. Such findings have led authors to propose fitness as a “protector and enhancer of cognitive function and CNS integrity” (Colcombe et al., 2003). Hence, changes in fitness may mediate the neurobiological changes that have been implicated in the exercise and cognitive function literature.

**Barriers to Exercising in MS**

Taken together, research suggests improving fitness via exercise may be a valuable method of enhancing cognitive function in MS. Despite several positive outcomes of exercise, most individuals with MS have low levels of daily physical activity (Motl et al., 2005; Stuifbergen, 1997), and research regarding potential cognitive benefits is relatively scarce. Lack of exercise in MS is reportedly due to limiting disease-related symptoms, such as fatigue, depression, motor and physical limitations, pain, and poor temperature regulation leading to overheating (Motl et al., 2005). However, as discussed, a lack of physical activity may actually lead to deconditioning and disuse that further exacerbates these symptoms and reduces functionality, indirectly worsening cognitive function (Mostert & Kesselring, 2002). Actually, exercise has been shown to improve the very symptoms that prohibit individuals with MS from engaging in exercise. In light of several positive outcomes, it is clear that exercise interventions for improving cognitive function must involve programs of effective intensity and duration, created with consideration for limitations in this population to facilitate accessibility and
adherence. Aquatic exercise is one type of program that may serve to overcome barriers and ensure optimal cognitive outcome in MS.

Aquatic Exercise in MS

**Overcoming barriers.** Aquatic exercise has been suggested in the literature for individuals with MS due to its feasibility and safety (Broach & Datillo, 2003; Coco, Maugeri, & Perciavalle, 2006; Plecash & Leavitt, 2014; White & Dressendorfer, 2004; Salem et al., 2011). This exercise modality may also address several of the barriers that are cited by individuals with MS. For example, the reduced physical impact offered by aquatic exercise may help to ease the motor symptoms and pain associated with MS. Moreover, low impact exercise such as this reduces the amount of energy expenditure required (Broach & Datillo, 2003) and may therefore reduce fatigue, another reported barrier to exercise in MS (Motl, Snook, & Schapiro, 2008). In addition, given that heat sensitivity and intolerance are also common exercise barriers in MS (Davis, Wilson, White, & Frohman, 2010) and that elevated body temperatures may aggravate pain, spasticity, and fatigue (Davis et al., 2010; White & Dressendorfer, 2004), aquatic exercise has been suggested specifically for thermoregulation in this sample (Döring et al., 2012, Petajan & White, 1999; White & Dressendorfer, 2004). Related to adherence, aquatic exercise allows for the delivery of interventions in group settings, which has been associated with more self-confidence (Hejazi, Soltani, Javan, Aminian, & Mehdi, 2012), improved mood and reduced levels of depression (Dodd, Taylor, Denisenko, & Prasad, 2006; Mostert & Kesselring, 2002), and greater exercise compliance (Petajan et al., 1996). In general, aquatic exercise may address
several of the barriers associated with lack of physical activity in MS, and may facilitate exercise participation and adherence in this group to ultimately ensure successful cognitive outcome.

**Fitness and cognitive improvements through aquatic exercise.** In addition to overcoming barriers, studies show aquatic exercise significantly improves various fitness measures in individuals with MS, including cardiovascular fitness (Gehlsen, Grigsby, & Winant, 1984; Petajan et al., 1996; Ponichtera-Mulcare, Mathews, Barrett, & Gupta, 1997). In addition, although effects have not been examined in MS specifically, this modality has demonstrated improved cognitive function in other populations, including older adults (Cancela Carral & Perez, 2007; Fedor, Garcia, & Gunstad, 2015) and persons with fibromyalgia (Munguia-Izquierdo & Legaz-Arrese, 2007). In these studies, improvements in cognitive function were noted in working memory, executive functioning, global cognitive function, attention, and memory, many of the domains affected in persons with MS.

Only one existing aquatic exercise study assessed changes in fitness alongside cognitive changes. This work demonstrated that cardiovascular fitness and performance on tests of executive function, attention, and memory improved following a very brief (1-week) daily aquatic exercise program in a group of older adults (Fedor et al., 2015); no significant improvement was noted in a matched control group. This study reported medium effect sizes for cardiovascular fitness changes, and medium-to-large effect sizes for changes in cognitive performance measured by domain-specific composite scores. While studies of individuals with MS have established that aquatic exercise can improve fitness, no study has directly examined an aquatic intervention targeting cognitive function. Given the effect sizes reported by Fedor and colleagues (2015), it is plausible that aquatic exercise could show similar results in MS.
Additionally, a brief intervention may be particularly advantageous in MS, given the possibility for sudden symptom exacerbation in individuals with the relapsing-remitting subtype.

In summary, MS is a neurodegenerative autoimmune disease of the central nervous system associated with several debilitating symptoms. Cognitive impairment is one such symptom that may exacerbate other symptoms and contribute to reduced quality of life. Research suggests exercise may be a useful tool for improving cognitive function in MS, and a review of the literature suggests fitness improvements could be a catalyst for these changes. In addition, the frequency and intensity of exercise appears to be important in improving fitness and cognitive function; however, given the scarcity of exercise studies in MS, no conclusions currently exist regarding necessary prescriptions for cognitive changes. In addition, existing studies in individuals with MS have been methodologically limited by lack of standardized exercise, failure to include a control group, failure to collect intensity or fitness measurements, small sample sizes, and limited cognitive measures.

Controlled experimental studies that incorporate exercise in a manner that is tolerable in this population are necessary to determine cognitive effects and deduce optimal “dosage” (i.e., frequency, intensity, duration). Aquatic exercise may be a valuable tool for overcoming barriers and facilitating participation in MS, and has been shown to improve fitness in MS and cognitive function in other populations.

The Current Study

Pilot data. The following pilot study was an examination of cognitive and fitness changes resulting from a weeklong daily aquatic exercise intervention. Pilot work of this protocol in five individuals with MS demonstrated that the exercise intervention produced
changes cardiovascular fitness (2-Minute Step Test, Cohen’s $d = 0.46$) and cognitive performance, including information processing speed ($d = 0.38$), cognitive flexibility ($d = 0.70$), and speeded inhibitory control ($d = 0.67$). Results from this pilot sample suggest that one week of daily aquatic exercise can produce cognitive and fitness changes in individuals with MS; however, examination in a larger sample with a control group comparison was deemed necessary to demonstrate that the positive impact observed in fitness and cognitive variables extends beyond practice effects.

**Aims and hypotheses.** To date, no prior work has examined the effects of a very brief aquatic exercise intervention on both fitness and cognitive function in MS. The current study examined these effects through the following aims and hypotheses:

**Aim 1: Determine the effects of a week-long aquatic exercise program on cardiovascular fitness in individuals with MS.**

*Hypothesis 1:* Participants in the exercise condition will demonstrate improved cardiovascular fitness from pre- to post-intervention, whereas those in the control condition will not.

**Aim 2: Determine the effects of a week-long aquatic exercise program on cognitive function in individuals with MS.**

*Hypothesis 2:* Participants in the exercise condition will demonstrate improved cognitive performance from pre- to post-intervention relative to those in the control group.
Aim 3: Determine whether changes in fitness mediate the relationship between group membership (i.e., exercise group versus control group) and post-test cognitive function.

Hypothesis 3. Fitness changes will mediate the relationship between group membership (i.e., exercise group versus control group) and post-test cognitive function, such that those in the exercise group will show greater cardiovascular fitness change and thus post-test cognitive function.

Aim 4: Examine the relationships between exercise intensity and changes in cardiovascular fitness and cognitive performance.

Hypothesis 4a: Exercise intensity, as measured by average heart rate and rate of perceived exertion, will be positively related to improvements in cardiovascular fitness.

Hypothesis 4b: Exercise intensity, as measured by average heart rate and rate of perceived exertion, will be positively related to improvements in cognitive performance.
CHAPTER II

METHODS

Design

The current study was a 2x2 (pre- versus post-intervention, exercise group versus no-exercise control group) pilot clinical trial assessing the effects of one week of daily moderate-intensity aquatic exercise on cardiovascular fitness and cognitive function in persons diagnosed with MS. Individuals took part in either an exercise group or non-exercise control group. Cognitive function and cardiovascular fitness were assessed at a pre-intervention baseline session and at a post-intervention session no sooner than 24 hours and no later than 48 hours after completion of the exercise protocol.

Participants

The study included 39 (19 exercise, 20 control) English-speaking individuals between the ages of 20 and 65 who were diagnosed with MS. One control group participant dropped out of the study following the pre-test, resulting in a total of 38 final participants (19 in each group; see Table 3 for a partial consort table).
Participants were recruited for the study from the Oak Clinic for Multiple Sclerosis (Uniontown, OH), Neurology and Neuroscience Associates (Akron, OH), local MS support groups and events, and local community businesses via study fliers. Participants were required to obtain approval from their physician prior to participating in the study. Exclusion criteria included: females who were pregnant or at risk for becoming pregnant, severe psychiatric illness (e.g., Schizophrenia, Bipolar Disorder), history of non-MS related neurological disorder or injury (e.g., seizure, brain injury), past or current history of alcohol or drug abuse, history of learning disorder or developmental disability, or sensory function impaired enough to preclude cognitive testing.

Measures

Neuropsychological test battery. Participants completed a brief battery of neuropsychological measures to assess function across multiple cognitive domains, including information processing speed, executive functioning, attention, and learning and memory. All measures utilized in the current study are included in the Minimal Assessment of Cognitive Functioning in Multiple Sclerosis (MACFIMS; Benedict et al., 2002, 2006), a neuropsychological battery designed to detect cognitive impairment in MS, and therefore have strong psychometric properties including high validity and reliability. The MACFIMS was created based on expert consensus, using literature with an eye toward psychometric factors and practical considerations (Benedict et al., 2006). The final tests included in the MACFIMS were judged to be the most sensitive to the cerebral pathology of MS (Benedict et al., 2006). Specific measures for the current study were chosen not only based on their known sensitivity to
cognitive dysfunction in MS, but also with consideration for minimizing practice effects and/or availability of alternate forms. Specific measures included:

**Delis-Kaplan Executive Function System (D-KEFS) Sorting Test** (Delis et al., 2001a).

The D-KEFS Sorting Test examines several important executive functions such as initiation of problem-solving behavior, concept-formation skills, cognitive flexibility, and the ability to inhibit previous sorting responses. In this test, participants are presented with six mixed-up cards that display both perceptual features (e.g., various shapes, lines, and colors) and printed words. Participants are asked to sort the cards into two groups with three cards per group in as many different ways as possible based on concepts or rules. Sorts are based upon verbal-semantic information from the printed words and on visual-spatial features and/or patterns on the cards, and there are eight pre-determined “confirmed correct sorts.” Upon sorting, participants must then describe the concepts employed to generate each sort. This test is then repeated with a second set of cards. Participants are allowed a maximum of four minutes for each card set and are asked not to repeat sorts. Alternate forms were administered at pre- and post-intervention assessments to minimize practice effects. The Sorting Test was chosen for the current study, as this test shows moderate to high test-retest reliability ($r \geq 0.46$) and high internal consistency ($\geq 0.77$; Delis et al., 2001c), and was specifically suggested for future investigations in MS by the panel that established the MACFIMS (Parmenter et al., 2007). In addition, previous studies have found that individuals with MS demonstrate impaired sorting accuracy and ability to explain sorting principles (Beatty & Monson, 1996), and poor performance on this test correlates with accumulation of lesions and other MRI variables in this population (Parmenter et al., 2007). To assess concept formation and cognitive flexibility, the current study utilized 1) total response
description scores (how well a participant describes the sorting principle), and 2) the number of “confirmed correct sorts,” or sorting pairs that have been predetermined to be correct.

**D-KEFS Trail Making Test** (TMT; Delis, Kaplan, & Kramer, 2001a). The D-KEFS TMT is based on the original Trail Making Tests (Reitan, 1992), but involves a series of five conditions rather than the two (A and B) in the original version. Condition 2 (Number Sequencing) of the D-KEFS version is analogous to TMT-A, which measures information processing speed by requiring participants to draw a line connecting numbers 1-16 in order while distractor letters appear on the same page. Condition 4 (Number-Letter Switching) is analogous to TMT-B, and measures set shifting ability by requiring participants to switch back and forth between connecting numbers and letters (i.e., 1, A, 2, B, etc., to 16, P) as quickly as possible. This task is not considered to be highly susceptible to practice effects, thus no alternate form exists (Delis, Kaplan, & Kramer, 2001b). The D-KEFS TMT has moderate test-retest reliability ($r \geq .38$; Delis et al., 2001c). The current study utilized only Conditions 2 and 4, as these are most comparable to the original TMT, which measure specific functions that have consistently been shown to improve following exercise (Fedor et al., 2015; Tanne et al., 2005). Time to completion (in seconds) was measured.

**D-KEFS Color-Word Interference Test** (CWIT; Delis et al., 2001a). The D-KEFS CWIT is a Stroop-like paradigm used to examine processing speed as well as a variety of executive processes, such as working memory, cognitive flexibility, and inhibitory capacity (Delis et al., 2001a). This test includes four conditions: Color Naming (Condition 1), Word Reading (Condition 2), Inhibition (Condition 3), and Inhibition/Switching (Condition 4) during which participants are instructed to name, as quickly as possible, visually presented stimuli presented in rows. In Condition 1, participants are first presented with patches of colors in red, green, and
blue. In Condition 2, the stimuli are the words “red,” “green,” and “blue.” These two conditions measure attention and information processing speed. In Condition 3, the individual is shown the names of colors printed in conflicting ink colors (e.g., the word “blue” in red ink) and is asked to name the color of the ink rather than the word. This condition measures ability to inhibit a response. Finally, in Condition 4, the stimuli are the same as in Condition 3, except that some words are enclosed in a box; in this case, the participant is instructed to name the word rather than the color of the ink that the word is printed in. This condition measures both cognitive flexibility and the ability to inhibit a dominant response (Wecker, Kramer, Wisniewski, Delis & Kaplan, 2000). Similar to the D-KEFS TMT, the CWIT is not among tests that are highly susceptible to practice effects and therefore has no alternate forms (Delis et al., 2001b). The CWIT has moderate-to-high test-retest reliability ($r \geq 0.62$) and good internal consistency ($\geq 0.72$; Delis et al., 2001c). The current study utilized total time to finish (in seconds) from each condition.

**Controlled Oral Word Association Test** (COWAT; Benton & Hamsher, 1976). The COWAT was used to measure phonemic verbal fluency. This test asks participants to generate words beginning with specified letters (F, A, S) of the alphabet for 60 seconds. Alternate forms (letters C, F, L) were administered to minimize practice effects. This test was chosen due to its strong psychometric properties, including high interrater reliability ($r \geq 0.90$) and test-retest reliability ($r = 0.84$). In addition, the COWAT has been positively correlated with greater physical activity (Brown et al., 2012). Total number of words summed across the three trials was used as the total score.
The California Verbal Learning Test-II (CVLT-II; Delis, Kramner, Kaplan, & Ober, 2000). The CVLT-II measures learning and memory. In this test, participants are required to learn a list of 16 words (List A) over the course of five trials. Following these learning trials, recall of a new 16-word list (List B) is assessed on an interference trial. Recall of List A is then immediately reassessed. Approximately 20 to 25 minutes after the learning trials, participants are administered a delayed free recall, delayed cued recall, and recognition trial (forced yes/no choice) for List A. An alternate version of the CVLT-II was administered to minimize potential practice effects. This test was chosen due to its high test-retest reliability ($r = 0.80$; Woods, Delis, Scott, Kramer, & Holdnack, 2006) and its validity as a measure of memory in individuals with MS (Stegen et al., 2009). Exercise has also been shown to improve CVLT-II performance in individuals with MS (Leavitt et al., 2014). Total number of words recalled across all learning trials as well as total delayed recall was used, as these variables have been suggested to be most sensitive to MS-associated cognitive impairment (Delis et al., 2000).

Cardiovascular fitness. In order to assess cardiovascular fitness, each participant completed the 2-Minute Step Test (2MST; Rikli & Jones, 1999). During this test, participants are asked to march in place for two minutes, raising the knees to the midpoint between the individual’s hip and knee. Past work supports the use of the 2MST as an accurate estimate of cardiovascular fitness (validity coefficient = 0.91, test-retest reliability = 0.88), and this measure has been associated with cognitive function in older adults (Rikli & Jones, 2002; Garcia et al., 2013). The number of times the right knee was raised to the required height in two minutes was used as a measure of cardiovascular fitness for the current study. Of note, three individuals who
exhibited difficulty on/could not complete the 2MST were noted in the database, and all analyses were examined with and without these participants.

**Self-report questionnaires.** Participants provided detailed educational, medical, neurological, and psychiatric history (e.g., anxiety and depressive symptoms) using self-report checklists. The Personal Health Questionnaire Depression Scale (PHQ-8) and Generalized Anxiety Disorder (GAD-7) were utilized to assess depressive and anxiety symptoms, respectively. Two questionnaires from the Multiple Sclerosis Quality of Life Inventory (MSQLI; Fischer et al, 1999), a battery consisting of 10 individual scales providing a quality of life measure that is both generic and MS-specific, were utilized to assess pain and fatigue symptoms: Pain Effect Scale (PES, 5-item version), and Modified Fatigue Impact Scale (MFIS, 5-item version).

**Rate of Perceived Exertion.** Rate of Perceived Exertion (RPE; Borg, 1982) is a self-reported scale that is used to measure feelings of effort, strain, discomfort, and fatigue experienced during exercise. Using the Borg 6-20 scale (Borg, 1982), participants indicated their intensity level by pointing out numerically where they fell on the scale (ranging from 6 “no exertion” to 20 “maximal exertion”). In the current study, RPE was assessed after the warm up, every 9 minutes throughout the exercise session (on Intervals 2, 4, and 6), and immediately after the cool down. These measurements were utilized to create an average for RPE each day. In addition, an aggregate of RPE across all seven exercise sessions was planned for use in the current study to determine average RPE achieved throughout the course of the intervention.

**Heart rate.** A Polar heart rate (HR) monitor was used to record resting HR during the first and final visits and to measure HR intensity during exercise sessions. Resting HR was used
to determine exercise training intensity as calculated through the Karvonen Method: \((220 - \text{age}) - \text{resting HR}\) to determine the HR reserve. The target HR was then determined with the following calculation: \(\text{[heart rate reserve x training %]} + \text{resting heart rate}\) (Karvonen, Kentala, & Mustala, 2007). During exercise, HR was monitored at the same time-points as RPE measurements. Participants were encouraged to work at 65-75% age adjusted maximum HR (moderate-to-high intensity) during exercise, and instructed to self-monitor HR and adjust intensity level as appropriate. Participants were monitored to ensure they did not exercise to exhaustion. HR was measured at the same time-points as RPE. Similarly, these measurements were also utilized to create an average for HR each day. In addition, an aggregate of HR across all seven exercise sessions was planned for use in the current study to determine average HR achieved throughout the course of the intervention.

**Disability.** A Multiple Sclerosis Functional Composite (MSFC; Cutter et al., 1999) score was calculated to assess disability and ensure both conditions (i.e., exercise and control groups) were functionally equal at the pre-intervention assessment. The MSFC is a three-part, standardized instrument that briefly assesses upper extremity, lower extremity, and speeded cognitive processing functions, expressed as a single score along a continuous scale. The MSFC has excellent intrarater reliability with an intraclass correlation coefficient of 0.90 (Cohen et al., 2001), and shows concurrent validity with the Expanded Disability Status Scale, a clinical assessment typically conducted by a neurologist and frequently used to measure disability in MS. The MSFC also correlates with MRI findings, including lesion load and brain atrophy (Fisher et al., 2000; Kalkers et al., 2001a, 2001b; Vrenken et al., 2007; Khaleeli, Sastre-Garriga, Ciccarelli, Miller, & Thompson, 2007; Rudick et al., 2001). Tasks included in the MSFC are the 9-Hole Peg
Test (9HPT), the 25 Foot Walk Test (25FTW), and the Paced Auditory Serial Addition Test (PASAT). The 9HPT (Kellor, Frost, Silberberg, Iversen, & Cummings, 1971) requires participants to move nine pegs into holes on a pegboard, and back into an open box. The 25FTW requires the participant to walk 25 feet as quickly and safely as possible; time is calculated from the initiation of the instruction to start and ends when the participant has reached the 25-foot mark (Kieseier, & Pozzilli, 2012). Finally, the PASAT (Gronwall, 1977; Lejuez, Kahler, & Brown, 2003) is a cognitive measure during which single digits are presented via audiotape every three seconds and the participant must add each digit to the one immediately preceding it. Performances on these three tasks are combined to create a single composite score reflecting the principal ways in which MS affects individuals (i.e., leg function/ambulation, arm/hand function, and cognitive function; Fischer, Rudick, Cutter, & Reingold, 1999).

**Exercise Intervention**

Aquatic exercise classes were held at 8:00 a.m. at the Kent State University Recreation Center. Sessions were conducted by certified trainers and monitored by first aid certified lifeguards. Each exercise class began with 10 minutes of warm-up exercises consisting of walking and stretching in the water. The warm up was followed by 40 minutes of exercise at 65-75% AAMHR (moderate-to-high intensity). This intensity was chosen as prior research has demonstrated its effectiveness in producing both changes in cardiovascular fitness and cognitive function in MS (Briken et al., 2013; Pilutti, 2012; Sandroff et al., 2015) and other populations (Baker et al., 2010; Blumenthal et al., 1989; Emery & Gatz, 1990; Kirk-Sanchez & McGough,
2014; Nagamatsu et al., 2013). Participants were encouraged to achieve and maintain this level of intensity.

The workout consisted of seven four-minute intervals of combined aerobic and resistance exercise, with each interval separated by a one-minute rest period. Intervals 1, 3, 5, and 7 focused on aerobic exercise consisting of structured walking/jogging at different speeds with or against the current. Interval 2 focused on upper body strength training by using the resistance of the water to complete shoulder lateral raises, chest flys, bicep curls, and triceps extensions. Interval 4 concentrated on lower body movements including abduction and adduction and hip flexion and extension. Interval 6 combined upper body and lower body movements and included more complex movements to mimic speed skating, hitting a punching bag, swinging a golf club, making a figure 8 and jumping jacks. Each class concluded with a 10 minute cool-down.

**Procedures**

All procedures were approved by the Kent State University Institutional Review Board. After prospective participants responded to fliers, they were called via phone by a researcher to provide them with information regarding the study, determine interest, and screen for inclusion and exclusion criteria. Participants were responsible for obtaining physician approval, demonstrated by signature on a document describing the nature of the intervention, prior to participating in the study. Individuals who met the inclusion criteria, did not exhibit any exclusion criteria, and were interested in participating were asked to visit the Kent State Exercise Physiology lab to sign an informed consent. In the event that an otherwise eligible participant reported color blindness that would interfere with ability to complete testing, this information
was marked in the participant’s file, and tests that would be impacted by this would not be administered.

The study took place over the course of nine days. Pre-intervention testing (day one) included the cognitive battery, self-report questionnaires, MSFC, 2MST, resting HR, and other physiological measures. All participants completed cardiovascular fitness testing prior to cognitive testing to ensure standardization and to reduce potential effects of cognitive fatigue on other measures. Further, in attempt to minimize order effects on cognitive testing, the order in which alternate versions of cognitive measures were administered was randomized. On days two through eight, participants in the exercise group completed the exercise protocol while the control group was instructed to maintain their regular level of activity. On day nine, all participants reported back to the lab to complete the same post-test measures (alternate forms where applicable) as on day one. Participants were randomly assigned to either the exercise or control condition whenever possible; however, given that MS is a low frequency diagnosis (2.5 per 100,000; World Health Organization, 2008), random assignment limited timely recruitment. Thus, while individuals who were available to participate in either group were randomly assigned, if an otherwise eligible participant could not attend daily exercise sessions for any reason, he or she was assigned to the control group. To counteract potential confounding effects due to assignment that was not fully randomized, demographic and baseline functional differences between the two groups were examined and controlled for as needed in all analyses.

**Statistical Power**

To calculate required sample size, an *a priori* power analysis was conducted based on the previously-described pilot data in a sample of five individuals with MS, as well as prior work in
older adults that utilized a similar aquatic exercise protocol (Fedor et al., 2015). As discussed, pilot data revealed positive changes in cardiovascular fitness (2-Minute Step Test, Cohen’s $d = 0.46$) and several measures of cognitive function, including information processing speed ($d = 0.38$), cognitive flexibility ($d = 0.70$) and speeded inhibitory control ($d = 0.67$) in individuals with MS. Additionally, Fedor and colleagues reported medium effect sizes for cardiovascular fitness variables (2-Minute Step Test, $d = 0.39$), and medium (0.31) to large (0.85) effect sizes for cognitive findings ($n = 27$). With $\beta = 0.80$ and a type I error rate of 0.05, a sample size of 19 participants in each group was determined adequate to detect similar effect sizes from pre- to post-intervention in the proposed study.

**Statistical Analyses**

**Preliminary Analyses.** In order to ensure data met assumptions associated with statistical models utilized (i.e., normality, linearity, and multicollinearity), normality tests and bivariate correlations were conducted prior to running analyses. Descriptive statistics and group comparisons using t-test and chi-square analyses were performed on baseline disability (i.e., MSFC score) and demographic variables (i.e., age, sex, and education), with the plan to control for any group differences in subsequent analyses. In addition, given their high comorbidity in MS as well as their propensity to affect cognitive performance, potential confounding factors (i.e., anxiety and depressive symptoms, fatigue, pain) at pre- and post-test were examined to assess for change, with intent to control for any significant differences between groups or over time. Medications were also reviewed, with the intent to control for use of medication with significant heart rate suppressing effects (e.g., beta blockers) as needed.
Primary Analyses

Aim 1. A two-way mixed Analysis of Covariance (ANCOVA) was used to compare scores on the 2-Minute Step Test (2MST) from pre- and post-intervention in individuals who completed the exercise program as compared to controls.

Aim 2. Two-way mixed Multivariate Analyses of Covariance (MANCOVAs) were used to determine changes in cognitive performance on D-KEFS measures (i.e., TMT, CWIT, Sorting Test), COWAT, and CVLT-II from pre- to post-intervention.

Aim 3. In the event of significant changes in cognitive tests and 2MST scores, bootstrap mediation was planned to determine whether changes in cardiovascular fitness mediated the relationship between group membership (i.e., exercise or control) and post-test cognitive function. Group membership (i.e., exercise or control) was included as the independent variable, changes in cardiovascular fitness was the mediator, and post-test cognitive function was the dependent variable. First, all variables were assessed for correlation with one another to determine their independent relationships. Each cognitive measure was then examined separately within its own mediation analysis. Bootstrapping analyses were conducted using a macro for SPSS written by Hayes (2012), as traditional methods for testing indirect effects (e.g., Sobel tests) have been demonstrated to suffer from a lack of power (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002).
**Aim 4.** Considering the possibility that the relationship between exercise intensity and cognitive performance/cardiovascular fitness may reflect a non-linear effect (i.e., “point of diminishing returns” or U-shaped curve effect), particularly in populations with chronic fatigue (LaManca et al., 1998), subjective and objective exercise intensity data were first plotted on a scatter plot (x-axis) with post-test cognitive function and post-test cardiovascular fitness (y-axis) to determine linearity between the two variables. These relationships appeared to be linear, thus, Pearson’s bivariate correlations were utilized for the following analyses.

*Variables utilized.* For the purpose of identifying all potential relationships between significantly improved cardiovascular fitness and cognitive measures and objective/subjective intensity (i.e., HR/RPE), both change scores (i.e., post-test performance – pre-test performance) and post-test values were analyzed to differentiate between the salience of amount of change versus final post-test cardiovascular fitness/cognitive performance. Importantly, RPE and HR data revealed consistent “peak” points in which higher HR and RPE were achieved. In order to capture potentially important changes in HR and RPE across each interval and each exercise day, intensity data were analyzed in the following ways to determine the relationship between objective/subjective intensity and cardiovascular fitness (Aim 4a) as well as cognitive performances (Aim 4b):

1. **7-Day Average.** This was calculated as the average of the mean HR/RPE measurements for each day (i.e., Day 1 mean + Day 2 mean + Day 3 mean,... etc., / 7). See Figures 8a and 8b for HR and RPE measurements across all seven days.
2. **Peak Day Average.** Day-by-day analysis of intensity was also conducted to examine how HR/RPE changed each day. Day 7 was determined to have the highest HR and RPE (i.e., the “peak day”) across all intervals; thus average HR and RPE at Day 7 was examined. See Figures 8a and 8b for HR and RPE measurements across all seven days.

3. **Peak Interval Average.** Similar to the above “peak day” analysis, all exercise session intervals were analyzed for the highest HR and RPE achieved each day. Interval 6 was determined to have the highest HR and RPE measurements (i.e., “peak interval”) across all seven exercise days; thus, average HR and RPE at Interval 6 across all seven days (i.e., Interval 6, Day 1 + Interval 6, Day 2 + Interval 6, Day 3, etc., / 7) were examined. See Figures 9a and 9b for HR and RPE measurements across all intervals throughout the exercise week.

4. **Peak Interval on the Peak Day.** Finally, given that HR and RPE were clearly highest on the final interval and on the final day, these two factors were combined: HR and RPE from Interval 6 on Day 7 were analyzed as well (i.e., HR/RPE at the peak interval on the peak day).

**Reliable Change Index.** Although the measures utilized in the present study were chosen for psychometric properties that suggest minimal practice effects, due to the short amount of time between assessments, a Reliable Change Index (RCI) calculation was planned in the event of cognitive and cardiovascular fitness changes, to determine whether they were reliably significant. RCI is one of the most commonly used methods of determining clinically significant
levels of change (Barker-Collo & Purdy, 2013). Given the possible influence of test-retest variability and practice effects on detecting true cognitive change, the RCI is utilized in research studies to facilitate interpretation of longitudinal neuropsychological data.

The RCI method has been utilized previously in MS samples (Barker-Collo & Purdy, 2013). Compared to other modalities of assessing for significant change, the RCI method is more conservative, and better accounts for practice effects and other sources of variance by incorporating the given measure’s test-retest reliability (Barker-Collo & Purdy, 2013). In the present study, the RCI was calculated as follows: $(X_2 - X_1)/S_{\text{diff}}$, where $X_1$ is the participant’s pretest score, $X_2$ the participant’s post-test score, and $S_{\text{diff}}$ is the standard error of difference, which utilizes the standard error of measurement and the test-retest reliability of the given measure (Hinton-Bayre, et al., 1999). Reliable change for the current study was defined as $\pm 1.645$ standard deviations based off of prior work in MS samples (Barker-Collo & Purdy, 2013). Chi-square analyses were conducted on RCI to determine if reliable change was statistically different between the exercise and control groups.
Preliminary Analyses

Assumptions. The following variables were not normally distributed and were successfully transformed: TMT-2 (Number Sequencing), D-KEFS CWIT-4 (Inhibition/Switching), MSFC scores, and GAD-7 scores. TMT-4 (Number-Letter Switching) scores could not be transformed using classic square root, logarithm, or inverse transformations, thus these data were interpreted with caution. For the purposes of clarity in interpretation, all data are presented in their original values.

Group comparison of demographic variables. Both the exercise and control groups were made up of similarly distributed MS subtype (control: 84.2% relapsing-remitting, 10.5% secondary progressive, 5.3% primary progressive; exercise: 84.2% relapsing-remitting, 5.3% secondary progressive, 5.3% primary progressive, 5.3% progressive-relapsing). Chi-square tests revealed no significant differences in MS subtype ($\chi^2 (2, N = 38) = 2.36, p = 0.66$), ethnicity ($\chi^2 (2, N = 38) = 3.30, p = 0.19$), or sex ($\chi^2 (2, N = 38) = 0.00, p = 0.67$) between groups.
Independent samples t-tests revealed exercise and control groups were also similar in duration of MS diagnosis, \( t(36) = -0.53, p = 0.59 \), age \( t(36) = -0.68, p = 0.49 \), and education \( t(36) = -0.68, p = 0.09 \). An independent samples t-test revealed no significant differences in baseline disability score (MSFC) between control and exercise groups at pre-test \( t(36) = -1.85, p = 0.08 \), suggesting that the groups had similar baseline functional ability. See Table 2 for group demographic information.

**Group comparison of potential confounders.** Independent samples t-tests of potential confounding variables revealed no differences in pain (PES; \( t(36) = -0.64, p = 0.52 \)), fatigue (MFIS; \( t(36) = -1.32, p = 0.19 \)), anxiety (GAD-7; \( t(36) = -0.03, p = 0.97 \)), or depressive symptoms (PHQ-8; \( t(36) = 0.89, p = 0.37 \)) between exercise and control groups at pre-test; scores on most of these questionnaires also remained statistically similar from pre- to post-test. However, paired samples t-tests revealed pain (PES) improved significantly for the exercise group \( t(18) = 2.48, p = 0.02 \) but not for the control group \( t(18) = 0.59, p = 0.56 \) from pre- to post-test. Thus, to be conservative, pre- and post-test PES scores were controlled for in all primary analyses. A review of medication lists for each participant revealed none were taking beta-blockers or other potentially confounding medications at the time of participation in the study, thus no medications were controlled for in the following analyses. See Table 2a for group comparisons of fatigue, pain, and anxiety and depression symptoms at pre- and post-testing.

**Primary Analyses**

**Aim 1:** Determine the effects of a week-long aquatic exercise program on cardiovascular fitness in individuals with MS.
A two-way mixed Analysis Of Covariance (ANCOVA) controlling for PES scores revealed an interaction effect between time and group membership on 2MST scores from pre-to-post testing \((F(1, 32) = 9.06, p = 0.01, \eta^2 = 0.22)\). Further analyses of simple main effects revealed significant group differences over time, such that the exercise group showed improved 2MST scores from pre-to-post \((F(1,15) = 20.65, p < 0.01, \eta^2 = 0.57)\), whereas the control group did not \((F(1,15) = 1.69, p = 0.21)\). See Table 3 for changes in 2MST means by group.

**Aim 2: Determine the effects of a week-long aquatic exercise program on cognitive performance in individuals with MS.**

No significant interaction effects (i.e., time by group membership) were noted on cognitive measures. However, a two-way mixed MANCOVA revealed a trend toward a significant interaction effect on total number of confirmed correct sorts achieved on the D-KEFS Sorting Test \((F(1,33) = 3.36, p = 0.07, \eta^2 = 0.09)\). A closer look at group means showed the direction of this trend was such that the exercise group improved slightly over time, while the control group remained relatively stable. See Table 3 for raw cognitive test values at pre- and post-test.

Although there were no other significant interaction effects among cognitive measures, there was a significant main effect of time on D-KEFS TMT-4 (Number-Letter Switching) scores: \((F(1,33) = 10.89, p < 0.01, \eta^2 = 0.24)\), suggesting faster performance for both groups over time from pre-to post-test. Similarly, there was a trend toward a main effect of time on D-KEFS CWIT-3 (Inhibition) scores: \((F(1,31) = 3.43, p = 0.07, \eta^2 = 0.10)\), suggesting a trend toward faster performance on this measure from pre-to post-test as well. Finally, there was a main effect
of time on COWAT performance \( F(1,33) = 8.29, p < 0.01, \eta^2 = 0.20 \), such that both groups improved significantly over time. There was no significant main effect of group membership for any of these cognitive measures.

In contrast to the noted improvements on the D-KEFS CWIT-3, TMT-4, and COWAT, a two-way mixed MANCOVA revealed a main effect of time on CVLT-II long-delay recall scores \( F(1,32) = 6.34, p = 0.02, \eta^2 = 0.16 \), with both exercise and control groups showing a similar decrease in performance from pre- to post-test. Likewise, there was a trend toward a main effect of time on CVLT-II total learning scores \( F(1,33) = 3.83, p = 0.05, \eta^2 = 0.10 \). A closer look at raw data showed the control group’s performance declined, while the exercise group remained relatively stable; however, significant group effects were not elicited on the CVLT-II. No other cognitive measures showed significant main effects or interaction effects. See Table 3 for changes in raw cognitive performance by groups.

**Aim 3: Determine whether changes in cardiovascular fitness mediate the relationship between group membership (i.e., exercise group versus control group) and post-test cognitive function.**

Given that there were significant changes in 2MST scores and cognitive tests from pre- to post-test, bootstrapping mediation analyses were conducted to determine whether improvements in 2MST mediated the relationship between group membership (i.e., exercise or control) and post-test cognitive performance. Pre- and post-test PES scores were included as covariates. Group membership was used as the independent variable, 2MST change score (i.e., post-test scores – pre-test scores) was used as the mediator, and post-test cognitive performance was used...
as the dependent variable for each cognitive test that showed improvement or a trend toward improvement (i.e., D-KEFS Sorting Test, TMT-4, CWIT-3, COWAT). CVLT-II learning and delayed recall scores were not included in meditational analyses, given the evident decline in or lack of change on these measures.

Analyses of meditational models revealed similar patterns for all cognitive measures examined. Specifically, for each cognitive test, group membership did not predict post-test cognitive performance. Group membership predicted 2MST change scores \( (b = 12.9532, SE = 4.1278, p < 0.01) \) for all cognitive measures. However, 2MST change scores did not predict performance for any post-test cognitive indices, thus meditation could not occur for any cognitive test. See Figures 4-7 for detailed information regarding these analyses.

This model was attempted again with post-test 2MST scores (as opposed to change scores) as the mediator variable, with the idea that perhaps a “threshold” level of cardiovascular fitness is needed for cognitive improvement (i.e., a certain “level” of fitness), rather than an overall change in fitness (Smiley-Oyen et al., 2008). However, this model proved to be a poor fit as well. Similar patterns were indicated: group membership once again did not predict post-test cognitive function, though there was a trend towards group membership predicting 2MST post-test scores \( (b = 17.55, SE = 8.81, p = 0.06) \). 2MST post-test scores did not predict any cognitive post-test scores. Overall, these findings suggest that although group membership predicted fitness change, the models utilized were not a good fit, and thus neither 2MST change nor 2MST post-test performances were successful mediators for the relationship between exercise and cognitive function in the current sample. See Figures 4a-7a for detailed information regarding these analyses.
Aim 4: Examine the relationships between subjective and objective exercise intensity and changes in cardiovascular fitness (4a) and cognitive performance (4b).

**Relationship between subjective and objective intensity data.** First, Pearson’s bivariate correlations were used to confirm a relationship between the study’s measures of objective and subjective intensity. However, the correlation between 7-Day Average HR and 7-Day Average RPE ($r = -0.25, p = 0.30$) was not statistically significant. Remaining analyses examining subjective and objective intensity also did not show significant correlations, including Peak Day HR and RPE ($r = -0.06, p = 0.78$), Peak Interval HR and RPE ($r = -0.35, p = 0.14$), and Peak Interval on Peak Day HR and RPE ($r = -0.09, p = 0.68$), suggesting poor correlation between subjective and objective measures of exercise intensity.

**Aim 4a. Cardiovascular fitness correlations with subjective/objective intensity.**

To remain consistent with analyses used in the above mediations (Aim 3), which considered both overall change scores as well as the potential “threshold” level of cardiovascular fitness, both change scores and post-test scores for 2MST and cognitive measures were utilized in the following analyses.

*Heart rate.* Post-test 2MST correlated with average 7-Day Average HR ($r = 0.49, p = 0.03$), as well as Peak Interval HR ($r = 0.50, p = 0.03$), Peak Day HR ($r = 0.49, p < 0.05$), and Peak Interval on the Peak Day HR ($r = 0.46, p = 0.04$). In contrast, there were no significant correlations between 2MST change scores and any measure of HR across the intervention. See Table 4 for a correlation matrix including 2MST, HR, and RPE measures.
Rate of Perceived Exertion. In regards to subjective intensity, no correlations were evident between any RPE measures and 2MST post-test or 2MST change scores. See Table 4.


Heart rate. Similar to the patterns noted with 2MST/intensity relationships, post-test cognitive performances were significantly correlated with objective measures of intensity. Specifically, post-test confirmed correct sorts on the D-KEFS Sorting Test correlated with 7-Day Average HR ($r = 0.47$, $p = 0.04$), Peak Day HR ($r = 0.50$, $p = 0.02$), and Peak Interval HR ($r = 0.48$, $p = 0.04$), such that greater scores were related to higher HR averages.

Likewise, D-KEFS CWIT-3 (Inhibition) post-test scores were correlated with 7-Day Average HR ($r = -0.68$, $p < 0.01$), Peak Interval HR ($r = -0.68$, $p < 0.01$), and Peak Day HR ($r = -0.64$, $p < 0.01$), suggesting faster speed of completion for this task with higher HR across all sessions, at Interval 6, and on Day 7. There were trends towards significant correlations between D-KEFS TMT-4 (Number-Letter Switching) post-test times and 7-Day Average HR ($r = -0.45$, $p = 0.05$) and across Peak Interval HR ($r = -0.46$, $p = 0.05$), suggesting a trend towards faster post-test performance on this test as well. Also in line with 2MST findings, change scores for cognitive measures did not show correlations with any measure of HR. See Table 4 for a correlation matrix including cognitive, HR, and RPE measures.

Rate of Perceived Exertion. Regarding subjective intensity, there were no correlations between any RPE measure and cognitive post-test performance or cognitive change scores. See Table 4.
Reliable Change Index

RCI calculations revealed reliable change in the exercise group from pre-to-post testing on the 2MST (36% of participants), number of confirmed correct sorts on the D-KEFS Sorting Test (5%), COWAT (11%), D-KEFS CWIT-3 (Inhibition; 6%), and CVLT-II delayed recall (10% declined). The percentages of reliable change in the control group from pre-to-post testing were overall lower: 2MST (5% of participants), Number of confirmed correct sorts on the D-KEFS Sorting Test (0%), COWAT (5%), D-KEFS CWIT-3 (Inhibition; 2%), with greater decline on CVLT-II delayed recall (21%). Neither group showed reliable change on TMT performances. Chi-square analyses of RCI revealed significant differences between exercise and control groups on 2MST changes ($X^2 (2, N = 38) = 6.36, p = 0.04$), suggesting reliable fitness changes were significant; however, RCI for cognitive measures were not significantly different between groups. See Figure 10.
The current study examined the effects of a weeklong aquatic exercise program on cardiovascular fitness and cognitive function in individuals diagnosed with MS. Cardiovascular fitness was investigated as a potential mediator for the relationship between group membership (i.e., participation in either the exercise or control group) and post-test cognitive function. In addition, the relationships between intensity during exercise and fitness/cognitive outcomes were examined. As expected, cardiovascular fitness improved following the intervention in the exercise group, but not in the control group. Cognitive function improved for both groups on various cognitive measures; however, performance on tests of learning and memory remained stable for exercisers, and declined in the control group, though significant group differences did not emerge. RCI showed that more individuals in the exercise group demonstrated reliable improvements on cardiovascular fitness and most cognitive measures (with the exception of memory); however, statistical comparison of RCI indicated only cardiovascular fitness showed significantly greater reliable change for the exercise group compared to controls, as groups did not significantly differ for any cognitive measures.
The proposed mediational models were not successful, given a lack of relationship between the analyzed variables. As a result, neither amount of fitness change nor total post-test fitness mediated the relationship between group membership (i.e., exercise vs. control group) and post-test cognitive function. Moreover, objective intensity measures (i.e., HR) correlated with post-test fitness and cognitive function. In contrast, subjective intensity measures (i.e., RPE) did not correlate with these variables, nor did they correlate with any measures of objective intensity. Several aspects of these findings warrant further discussion.

One Week of Exercise Improves Cardiovascular Fitness

Consistent with our hypothesis, cardiovascular fitness improved from pre-to post-test in the exercise group, but not in the control group. RCI analyses supported this finding, as the percentage of individuals demonstrating reliable improvement in cardiovascular fitness measures was significantly greater in exercisers. These findings extend past research: the few existing studies that have examined the effects of aquatic exercise on fitness in MS have shown benefits comparable to those of land-based exercise interventions (Briken et al., 2013; Mostert & Kesselring, 2002). However, this is the first study to examine effects following such a brief intervention, and results are suggestive of fitness benefits following a relatively short period of time. Given the positive factors associated with higher fitness in MS (Prakash et al., 2007; Sandroff & Motl, 2012; Prakash, Snook, Motl, & Kramer, 2010), results of this study warrant the investigation of intermittent exercise (Cooper et al., 2016; Mattson, 2014; Thompson et al., 2015) for the purpose of improving cardiovascular fitness while accommodating the periodic
symptom exacerbation common in MS. Future work to confirm the effects of intermittent exercise on fitness noted in this study is important.

Cognitive Changes not Significantly Different Amongst Control and Exercise Groups

While findings of improved cardiovascular fitness in the exercise groups were robust, cognitive outcomes were more variable. Of note, a potential confounding factor was present: self-reported pain levels improved significantly from pre-to-post testing in the exercise group, but not in controls. Although this finding was not specifically proposed, it was not entirely unanticipated. Aquatic-based therapies are often used to manage pain in clinical samples (Castro-Sanchez, et al., 2011), and the finding that pain improved following exercise in the current study supports the notion that exercise can help reduce pain in MS (Bjarnadottir, et al., 2007; Döring et al., 2012; Gallien et al., 2007; Motl, et al., 2009; Sá, 2014; White & Dressendorfer, 2004). At the same time, given the postulated relationship between pain and cognitive function (Sahraian & Etesam, 2014), it can be difficult to discern the amount of cognitive change attributable to improved pain versus other mechanisms, (e.g., improved cardiovascular fitness), unless analyses control for this factor. As such, pre- and post-testing pain scores were utilized as covariates in all analyses for the current study. This approach may have precluded identification of stronger, statistically significant cognitive changes, but this finding also represents an important relationship to further investigate in order to elucidate the relationship between pain and cognitive function.
Despite conservative approaches to control for confounders, there were positive cognitive findings. Although there were no significant interaction effects (i.e., time by group) for cognitive measures, a trend toward a significant interaction effect for the number of confirmed correct sorts on the D-KEFS Sorting Test emerged. All other cognitive changes following the intervention were either non-significant, or were significantly different for both groups with no between-subjects effects, suggesting both groups showed improved cognitive performances. RCI analyses, which account for a given measure’s test-retest reliability, were then utilized to determine whether change in cognitive performance was reliable, even if not statistically significant. RCI analyses showed that a larger percentage of individuals in the exercise group exhibited reliable cognitive improvements relative to controls, and a larger percentage of individuals in the control group showed reliable decline in memory tasks. However, direct comparisons of RCI indicated these reliable cognitive changes were not statistically different between groups.

Our lack of statistically significant group differences on cognitive measures could be explained by several potential phenomena. First, despite the use of alternate forms where available (i.e., CVLT-II, Sorting Test, COWAT), practice effects appear to have occurred for many of these measures. Susceptibility to practice effects is typically analyzed following a much longer period of time between testing intervals than in the current study (Dikmen et al., 1999). Thus, one week may simply not have been sufficient time to avoid practice effects.

Moreover, given our relatively small sample size, the finding that both groups improved cognitively appear to be partially attributable to insufficient statistical power, rendering it difficult to find significant interaction effects and/or between-group differences. This was
evidenced by the finding of many “trends” toward significance on cognitive measures. RCI findings (i.e., the fact that reliable cognitive changes were not statistically different between groups) further implicate a lack of statistical power in the current sample, as results tended to demonstrate a pattern in the expected direction, but failed to reach a level of significance statistical difference between groups. While a priori power analyses suggested our sample size was adequate to detect changes, this was based on prior work in a different population--healthy other adults--which may not optimally predict outcomes in an MS sample. Effects noted in the current study, which ranged from small to medium, were smaller than the medium to large effects anticipated based on our pilot work with individuals diagnosed with MS. Indeed, based on observed effect sizes for the current study, a much larger sample size (i.e., 80-120 participants) would have been required to determine significant cognitive differences (See Table 3). Collectively, these outcomes suggest that although there were reliable cognitive changes following the exercise, the effects were too small to be detected, and may not be clinically meaningful at an individual level.

In addition, it is possible that this study was susceptible to demand characteristics (Orne, 2009), especially in light of our quasi-experimental method of group allocation. Participants in the current study were provided full disclosure about the intent of the study, and thus may have been inclined to live up to the experimenters’ expectations or attempt to demonstrate intact cognitive function despite their diagnosis by performing at a higher standard than they typically would. These potential predispositions may have skewed findings such that some participants, particularly those in the control group who did not have the option to participate in the exercise,
may have been motivated to demonstrate that they were cognitively intact regardless of an intervention.

Finally, relative to significant group differences in cognitive function that are frequently demonstrated following exercise interventions in older adults, including prior work using the same one week aquatic exercise utilized in the current study, our modest cognitive changes could reflect that cognitive function in MS is more resistant to change via increased exercise/cardiovascular fitness compared to older adults. Given the differences in etiology and pathology (Feinstein, 2011), it is possible that this neurological population does not benefit from exercise in the same way as cognitively healthy samples (e.g., older adults). Future work is necessary to determine if exercise can show similar cognitive benefit in MS, and if so, to examine possible modifications (e.g., varying type, dose, and duration) that may be required in order to induce positive cognitive effects in this specific population.

Performances on tests of learning and memory produced different patterns than other aspects of cognitive function. Specifically, in the control group, performance actually declined on CVLT-II delayed recall, while the exercise group remained relatively stable; however, there were no significant group differences on these measures. Similarly, RCI calculations suggested that although reliable change was observed in both groups, they did not significantly differ from each other. There was also a trend toward a significant decline over time in CVLT-II learning scores. In light of the fact that this measure showed a different pattern from all other cognitive tests, it is plausible that exercise does not affect memory in the same way as complex attention and executive functions. Differential effects might be expected, given the way exercise impacts specific brain regions and associated cognitive processes. For example, the selective
improvement hypothesis (Kramer et al., 1999) of exercise proposes that exercise leads to selective, as opposed to generalized, cognitive benefits. Specifically, executive-based tasks associated with the frontal lobe are expected to show the largest improvements following exercise. In accordance with this theory, cognitive processes that are not executively-based are less likely to benefit from exercise (Kramer et al., 1999).

Different underlying mechanisms may be responsible for these region-specific effects. For example, in aging samples, it has been shown that rapidly occurring exercise-induced changes such as increased cerebral blood flow and oxygenation (Brown et al., 2010; Davenport et al., 2012; Lucas et al., 2012; Querido & Sheel, 2007), typically impact cortical regions to a greater extent (Davenport et al., 2012). This phenomenon is thought to occur due to the greater pliability of these structures (Erickson & Kramer, 2009), likely resulting in increased growth of blood capillaries (Ainslie et al., 2008; Churchill et al., 2002). It is therefore possible that short-term exercise interventions, such as the one implemented in the current study, are better able to capture improvements in cognitive functions related to these regions given the speed with which they occur (Davenport et al., 2012; Garcia & Gunstad, 2015; Querido & Sheel, 2007). In contrast, the aging literature demonstrates that exercise-induced changes in memory have been consistently associated with structural changes and increased neurogenesis in the hippocampus (Colcombe et al., 2006; Erickson et al., 2011), more gradual mechanisms of change (Davenport et al., 2012; Garcia & Gunstad, 2015; Querido & Sheel, 2007). Consistent with this notion, these subcortical regions consistently show positive changes following longer-duration exercise in older adults (Davenport et al., 2012; Erickson et al., 2011).
Overall, it is plausible that different mechanisms for improved cognitive function are at play in these brain regions and their related cognitive functions. Exercise of longer duration may have thus captured improved memory in this sample; however, although results from the current study point towards patterns of cognitive change, we were unable to capture significant group differences on any cognitive domain. Despite the lack of significant change in our sample, given that two studies (Briken et al., 2013; Leavitt et al., 2013) have shown memory improvements in MS following longer exercise interventions (i.e., >12 weeks), further research is required to delineate the pattern of change in learning and memory versus other domains following exercise.

Proposed Mediation Models for Relationship between Exercise, Fitness, and Cognitive Function were Not Confirmed

Collectively, fitness changes from pre- to post-testing were in line with our hypotheses, but hypotheses regarding cognitive improvement were not fully supported. In contrast to our predictions, meditational models were thus not confirmed. It appeared that our hypothesized model was not a good fit, as not all three variables included in the model correlated with each other. Specifically, group membership (i.e., exercise versus control) predicted cardiovascular fitness changes. However, fitness changes did not correlate with post-test cognitive function, nor did post-test cognitive function correlate with group membership. Further, when approaching this model from a threshold emphasis, rather than a theory of overall change (i.e., using post-test 2MST rather than 2MST change), similar patterns emerged: there was a trend toward group
membership predicting post-test fitness, but once again, post-test fitness and post-test cognitive performance were not related, nor were post-test cognitive performance and group membership. The lack of correlations renders the proposed meditational models theoretically incorrect, thus it is not surprising that the models were not supported. It is likely that cognitive changes in this study were not robust, thus limiting their relationship with 2MST findings.

Alternatively, although a large body of research supports the cardiovascular fitness hypothesis, some studies suggest that cardiovascular fitness is not a determining factor for cognitive performance (Etnier et al., 2006). In light of the current findings, other mechanisms potentially underlying the relationship between exercise and cognitive function, such as clinical variables (e.g., pain), and neurobiological responses (e.g., neuronal growth, increased brain volume, functional brain changes) may be more important variables to consider.

*Objective, not Subjective Exercise Intensity is Related to Cardiovascular Fitness and Cognitive Function*

Despite the lack of correlation between cardiovascular fitness changes and cognitive performance, analyses of relationships between various measures of intensity, fitness, and cognitive variables revealed remarkable patterns. First, various measures of objective intensity correlated with post-test fitness and post-test cognitive function (as opposed to total change in fitness or cognitive function). However, subjective intensity measures did not correlate with these variables, nor did they correlate with any measures of objective intensity, suggesting a discrepancy between participants’ perception of exertion and their physiological exertion. These findings raise an important point for exercise programs in MS: given high instances of autonomic
dysfunction in the disease (Adamec & Hamek, 2013), individuals with MS can experience symptoms that may alter the sense of exertion (e.g., fatigue and heat sensitivity; Morrison et al., 2008) and result in incongruities between objective measurements and subjective report of exertion. This finding warrants further examination of the benefits of utilizing various exertion measures in studies assessing fitness/cognitive change in MS.

The finding that post-test cardiovascular fitness and post-test performance on various cognitive measures significantly correlated with most measurements of objective intensity indicate that exercise intensity may be directly related to final achieved fitness or cognitive performance, rather than an absolute value of change in either of these domains. As an example, depending on their baseline level of fitness, two participants may show differing amount of change but achieve the same 2MST score at post-test; this final 2MST score may be more reflective of the higher achieved intensity during exercise. These findings collectively point toward the notion that higher intensity is related to greater end-point cardiovascular fitness and cognitive performance, rather than an overall change in either of these variables.

Moreover, the finding that final interval and final day HR measures were related to cognitive and cardiovascular fitness outcomes point to a cumulative effect, such that higher objective intensity as a result of exercise duration/session accumulation is related to greater cardiovascular fitness and cognitive outcomes. The positive associations with higher objective intensity noted in the current study are consistent with existing studies in MS samples (Briken et al., 2013; Pilutti, 2012; Sandroff et al., 2015), and other populations (Blumenthal et al., 1989; Emery & Gatz, 1990; Kirk-Sanchez & McGough, 2014, Baker et al., 2010; Nagamatsu et al., 2013, Palleschi et al., 1996), in which interventions of moderate-to-high intensity (e.g., 60 to 80 percent of
maximum heart rate) are consistently successful in producing fitness and cognitive changes. These studies collectively indicate this may be an important intensity threshold to reach during exercise. Results of the current study support the concept that higher objective intensity is related to greater fitness and cognitive function.

Clinical Implications

The current findings generate important clinical implications for individuals with MS. Although past work has demonstrated benefits of long-term exercise, the current study suggests that just one week of moderate intensity aquatic exercise can improve cardiovascular fitness in this population. Although cognitive changes were not significant, patterns of increased cognitive performance warrant future research to clarify these effects. Findings also warrant additional exploration of short-duration intermittent exercise, which has been increasingly recognized for fitness and cognitive benefits in other populations (Cooper et al., 2016; Mattson, 2014; Thompson et al., 2015). This avenue is particularly worth exploring in clinical populations such as MS, in which periodic exacerbation of debilitating symptoms may prohibit chronic, long-duration exercise training.

Of additional importance is the finding that exercisers reported significant decreases in pain. Given the high incidence of pain in MS (Solaro, Trabucco, & Uccelli, 2013), aquatic exercise could reduce the burden of such a substantial barrier in this population. This advantage, in conjunction with how well-tolerated the current intervention appeared to be, may increase the likelihood that individuals with MS would engage in physical activity, ultimately decreasing
functional and cognitive decline. Overall, these findings shed light on important considerations for future exercise interventions in MS.

**Strengths and Limitations**

Though findings point toward many positive effects of brief, moderate intensity aquatic exercise in MS, the current study is not without limitations. First, while random assignment was incorporated as often as possible, several prospective participants could not commit to the full protocol for various reasons, including lack of transportation, work schedule, and distance. Thus, to facilitate timely recruitment, eligible individuals were given the option to participate in the control group if they were unable to attend the daily exercise sessions, but could commit to the two testing sessions. This self-selection of some participants may have skewed results due to naturally occurring differences. For instance, participants who were unable to attend exercise sessions due to working full-time may be less functionally and/or cognitive impaired, both of which are related to unemployment in this population (Rao et al., 1991). On the other hand, individuals who self-selected the control group due to lack of transportation may actually be more impaired, as reflected by their greater need for assistance (i.e., inability to drive). The lack of significant differences in baseline disability (i.e., MSFC) between groups helped to reduce bias in this respect, though we cannot entirely rule out that potential functional differences at baseline not detected by our disability measure could have impacted outcomes.

Another important limitation of the current study is sample size. As previously discussed, several findings of trends toward significance for cognitive changes suggest a lack of statistical power. Effect sizes noted in the current study were reflective of limited power, and suggest a
much larger sample size was necessary to determine significant cognitive differences. Although prior similar work in older adults (Fedor et al., 2015) suggests our sample size of 38 should have been sufficient to detect medium to large effect sizes, these populations are not equivalent; patterns of cognitive impairment in older adults are not parallel with those in MS, as aging is not a pathological process associated with the degree of physical disability and brain changes found in MS (Feinstein, 2011). Thus, similar programs might be expected to have less robust effects on neurologic populations (i.e., MS), in which the goal may be reversing cognitive pathology, rather than preventing onset of impairment. While studies in older adults provide a foundation for building exercise interventions in MS, it is evident that a larger sample size would be necessary to determine changes in this cognitively distinct group. Perhaps more important, though, is the issue of degree to which any cognitive changes detected are clinically meaningful. If effects are this small, one must consider how much impact they would have on the daily functioning of the individual. This raises the idea that a different dose of exercise might be needed to achieve effects great enough to be both statistically significant within a reasonably sized sample, as well as clinically meaningful to the individual.

Despite notable limitations, the current study also has several key strengths. To our knowledge, this is the first study to examine the effects of a week-long aquatic exercise intervention on cardiovascular fitness and cognitive function in MS. Given some of the barriers cited for exercise in this population, such as fatigue (Motl et al., 2005), intermittent (rather than continuous) moderate intensity exercise may be advantageous. For example, intermittent exercise may be beneficial for individuals with MS who are prone to relapses (Karpatkin et al., 2015; Mattson, 2014), as they may not be able to maintain a prolonged long-term exercise
regimen due to symptom flare-up. Moreover, the findings that symptoms were not exacerbated by the exercise, and that pain actually decreased significantly in the exercise group, suggest that this level and duration of activity was well tolerated by participants.

Similar to the few successful exercise intervention studies in MS (Briken et al., 2013; Leavitt et al., 2013; Sandroff et al., 2015), the current study utilized moderate intensity exercise and found associations between objective intensity, cardiovascular fitness, and cognitive function. However, this study differs from past intervention studies in that it was successful in detecting improved fitness following just one week of exercise training in MS. Successful long-term studies have employed biweekly interventions for 12 to 24 weeks (Briken et al., 2013; Leavitt et al., 2013), while our study occurred for seven consecutive days during a single week. Further, despite a lack of significant differences, several trends toward improved cognitive function suggest future studies with larger samples and/or different exercise programs may be more likely to achieve cognitive improvement. The current study also suffered fewer methodological limitations compared to prior work, such as low adherence, lack of standardized exercise, and failing to assess fitness as an objective measure of exercise-induced changes. This study therefore meaningfully contributes to the literature on MS, exercise, and cognitive function.

Future Research

Future studies should conduct similar interventions in larger samples, which may offer greater statistical power. The finding that our one-week moderate-intensity intervention improved cardiovascular fitness certainly warrants further investigation of the benefits of intermittent aquatic-based exercise in MS. Given the lack of statistically significant differences in reliable change in cognitive function, it will be important to determine ways in which exercise
could be modified (e.g., varying type, dose, and duration) in order to induce positive cognitive effects in this specific population. Future research may also wish to explore additional potential mechanisms underlying the relationship between exercise and cognitive function in MS, as this population may not respond to increased exercise or improved fitness in the same manner as cognitively healthy groups. Along these lines, the incorporation of pain measures should be considered to allow for examination of changes and contributions to cognitive function. In addition, given the different presentations and trajectories of the four MS subtypes (Brissart et al., 2013), future studies should consider exploring effects in each subtype separately to allow for comparison. Finally, prospective exercise interventions in MS should assess both the reliability of, and discrepancies between, reporting subjective and objective intensity experiences, to better understand their influences on study outcomes.

Conclusion

In summation, the current study illustrates individuals with MS who participated in just one week of moderate intensity aquatic exercise showed greater cardiovascular fitness changes compared to a control group. Raw values of cognitive performance showed possible small cognitive changes as well, though group differences were not statistically significant, suggesting improvements may have been due to practice effects. Our proposed mediational models were not supported, likely due at least in part to the relatively small magnitude of cognitive change, resulting in limited ability to determine relationships between variables. Greater objective intensity throughout exercise, as measured by heart rate averages, was related to better fitness/cognitive outcomes. In contrast, measures of subjective intensity did not correlate to these
outcomes nor to objective intensity. Additional work in larger sample sizes is necessary to confirm the current findings and identify different forms of exercise or other possible mechanisms involved in the relationship between exercise and cognitive function. Findings from the current study provide a foundation for future work examining potential fitness and cognitive benefits of intermittent aquatic exercise in MS.
REFERENCES


