EFFECTS OF BRIEF AQUATIC EXERCISE IN MULTIPLE SCLEROSIS ON MOBILITY AND FUNCTION

A dissertation submitted to the Kent State University College of Education, Health, and Human Services in partial fulfillment of the requirements for the degree of Doctor of Philosophy

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BACKGROUND: Multiple sclerosis is a demyelinating disorder that impacts mobility and function. The benefits of exercise on multiple sclerosis symptoms have been demonstrated. Exercise is proven to increase cerebral blood flow, and improve oxygen utilization which may potentially help in counteracting the hypometabolic component of multiple sclerosis. However, barriers to exercise in people with multiple sclerosis limits their participation in long term exercise. PURPOSE: The purpose of this investigation was to determine the effects of a 7 consecutive day aquatic aerobic exercise intervention on mobility, fitness, body composition, and self-efficacy. A further purpose of this investigation was to determine the effects of the exercise intervention on cerebral oxyhemoglobin, deoxyhemoglobin, and % tissue saturation index (%TSI). METHODS: Twenty-one individuals diagnosed with multiple sclerosis were assigned to the exercise group or the non-exercise group. Both groups participated in a pretest and post-test separated by 7 days. The pre/post-test anthropometric measures included height, weight, BMI, hip and waist circumference measures. In addition, blood pressure, mean arterial pressure, body temperature, and resting heart rate were recorded. Mobility was assessed through the timed up and go test (TUG) and the 25-foot walk test (T25-FW), and fitness was assessed through the 2-minute step test. The Multiple Sclerosis Self-Efficacy questionnaire was used to assess self-efficacy. Oxyhemoglobin, deoxyhemoglobin, total
hemoglobin and % TSI were measured using Near-Infrared Spectroscopy (NIRS). The non-exercise group was asked to maintain their lifestyle during the 7 days between the pretest and post-test, while the exercise group participated in 1 hour of aquatic aerobic exercise for each of the 7 days between the pretest and post-test. Change scores were calculated for each variable of the pretest and post-test and the non-exercise and exercise groups were compared using independent samples t-tests for each of these scores.

**RESULTS:** Although there were no statistically significant differences between the exercise and non-exercise groups for mobility, fitness, body composition, self-efficacy, or cerebral oxygenation, there were small clinically meaningful improvements. In mobility (T25-FW), 8/11 exercise participants improved while only 1/9 in the non-exercise group showed improvement. Similar small improvements were demonstrated in the two minute step test used to assess fitness. Cerebral oxygenation also showed improved blood flow through improved oxyhemoglobin and total hemoglobin and improved oxygen utilization through the deoxyhemoglobin response. **CONCLUSION:** Seven consecutive days of moderate intensity exercise can produce small clinically meaningful changes through improved mobility, fitness, self-efficacy and cerebral oxygen utilization.
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CHAPTER 1
INTRODUCTION

Background

Multiple sclerosis (MS) is the leading cause of non-traumatic neurologic disability in young adults (Solari et al., 1999). The prevalence rate in the United States is 1/1000 and 2.1 million individuals suffer from multiple sclerosis worldwide (Marck and colleagues, 2014; Dibble, Lopez-Lennon, Lake, Hoffmeister, & Gappmaier, 2013). MS is caused by demyelination of axons, focal plaque formation, and inflammation in the central nervous system which results in progressive loss of function. In addition, MS has hypometabolic pathology consisting of decreased oxygen utilization and decreased absolute cerebral blood flow (Sun, Tanaka, Kondo, Okamoto, & Hirai, 1998; Brooks, et al., 1984). The location of pathology results in varying combinations of symptoms which include fatigue, heat sensitivity, muscle spasms, gait problems and ataxia, dizziness and vertigo, pain, cognitive problems, visual complaints, and bowel and bladder dysfunction (Anthony, Jouria, & Houtman, 2014).

Forms of MS are characterized by specific onset and symptoms of the disease process. Progressive forms of MS display continual worsening of symptoms, whereas relapsing-remitting (RRMS) forms of MS exhibit exacerbations of symptoms followed by resolution. The symptoms occur when demyelination and inflammation prevent the axons from conducting impulses to and from the central nervous system to the periphery. For the first few demyelinating events, the central nervous system is able to remyelinate
the axons, restoring conduction and the symptoms subside (Brown, Narayanan, & Arnold, 2014). However, as the disease progresses, the ability of the central nervous system to compensate diminishes. Although there is no cure for MS, pharmacological and rehabilitative treatments aim to slow the progression of the disease and prevent relapses, and to treat the symptoms.

Compounding the impact of the disease, symptoms resulting from MS pathology are correlated with decreased levels of physical activity (Hayes, Gappmaier, & LaStayo, 2011; Marck et al., 2014) and subsequent deconditioning that reduces quality of life (Doring, Pfueller, Paul, & Dorr, 2012). Further fallout from decreased physical activity includes diminished leisure activities, social contacts, activities of daily living, as well as lowered self-efficacy (Reitberg, Brooks, Uitdehagg, & Kwakkel, 2011). Physical and cognitive impairments strongly influence the level of independence in the MS individual (Langdon & Thompson, 1999), and physical activity can be used as a goal oriented, multidisciplinary approach to improve function (Rietberg, van Wegen, Kollen, & Kwakkel, 2014).

The primary aim of rehabilitation is to increase activity levels as well as the independence of MS individuals (Langdon & Thompson, 1999), through success in decreasing fatigue (Asano & Finlayson, 2014), improving cognition (Briken et al., 2014; Prakash, Snook, Motl, & Kramer, 2010), improving mobility (Pilutti, et al., 2011; Kargarfard, Etemadifar, Baker, Mehrabi, & Hayatbakhsh, 2012), improving physical
functioning and easing psychosocial burden (White, Castellano, McCoy, Patel, & Giacobbi, 2012).

**Rationale**

It was once thought that exercise exacerbated MS symptoms and was contraindicated in this population (Hayes, Gappmaier, & LaStayo, 2011). As exercise increases body temperature, central pathways become blocked, producing temporary physical and cognitive symptoms (Davis, Wilson, White, & Frohman, 2010). Worsening symptoms depend on location of the demyelination and lesions, and frequently include deficits in mobility, memory retrieval, processing speed, multitasking, and increased fatigue (Davis, Wilson, White, & Frohman, 2010). However, current research supports the positive effects of exercise in MS treatment, including improved fitness benefits, feelings of well-being, strength and safety of mobility and decreased fatigue (Davis, Wilson, White, & Frohman, 2010; Rietberg, Brooks, Uitdehagg, & Kwakkel, 2011).

Adverse effects during MS exercise were slightly higher when compared to non-exercising individuals (Pilutti, Platta, Motl, & Latimer-Cheung, 2014). However, these adverse effects were not greater than in healthy individuals who exercised (Pilutti, Platta, Motl, & Latimer-Cheung, 2014). Exercise training is associated with a slight decrease in the risk of relapse when compared to non-exercising MS individuals (Pilutti, Platta, Motl, & Latimer-Cheung, 2014). Exercise also has the capacity to slow disease progression, improves the physiological profile of MS and is well tolerated with a low occurrence of adverse effects (Kargarfard, Etemadifar, Baker, Mehrabi, & Hayatbakhsh, 2012).
Current research has established the hypometabolic impact of MS (Fan et al., 2015; Sun, Tanaka, Kondo, Okamoto, & Hirai, 1998; Brooks et al., 1984; Kidd et al., 1999; Bakshi, Miletich, Kinkel, Emmet, & Kinkel, 1998), however few studies have used Near Infrared Spectroscopy Systems (NIRS) to monitor cerebral oxygenation levels in MS (Lintas, Molinari, Simonetti, Franzini, & Liboni, 2013). There are no studies to date that have used NIRS to determine the impact of exercise on cerebral oxygenation in MS, though exercise has the potential to increase oxygenation through increased blood flow and improved oxygen utilization (Ide & Secher, 2000; Rooks, Thom, McCully, & Dishman, 2010).

Several studies have demonstrated positive effects of exercise on gait parameters and quality of life using 4 weeks of exercise training, however, no studies to date have used 7 consecutive days of exercise (van den Berg et al., 2006; Mostert & Kesselring, 2002). Previous work done by Fedor (2014) produced positive results in fitness and cognitive parameters in a similar aquatic aerobic seven consecutive day exercise protocol in older adults. RRMS forms of MS may benefit from high intensity, short duration exercise between relapses. However, the potential benefits of 7 consecutive days of exercise on cardiovascular fitness, and symptoms including self-efficacy and fatigue in MS are unknown.

**Objective**

MS individuals have been shown to have lower physical activity levels compared to healthy individuals (Rietberg, van Wegen, Kollen, & Kwakkel, 2014). Decreased
activity levels lead to a cascade of decreased mobility, balance, quality of life, self-efficacy, and deconditioning (Kuspinar, Anderson, Teng, Asano, & Mayo, 2010). Exercise has been found to lower oxygen consumption and heart rate; increase oxygen pulses at a given work rate and improve the aerobic system (Mostert & Kesselring, 2002). Kargarfard and colleagues (2012) found exercise training programs are associated with small clinically meaningful improvements in mobility of walking in MS individuals. Determining the role of 7 days of consecutive aquatic exercise program will assist medical professionals in optimally using exercise for treatment in MS. The objective of this project is to quantify changes in mobility, cardiovascular fitness, and cerebral oxygenation parameters in order to determine if seven consecutive days of aquatic aerobic exercise can provide benefits of fitness and mobility in MS individuals.

In this study we will be testing the following hypotheses:

1. A seven day moderate to high intensity water aerobics program will improve mobility, as measured by the Timed Up and Go Test (TUG), and Timed 25 Foot Walk Test (T25FW) in individuals with MS.
2. A seven day moderate to high intensity water aerobics program will improve cardiovascular fitness, as measured through resting heart rate and 2 Minute Step Test in individuals with MS.
3. A seven day moderate to high intensity water aerobics program will improve Cerebral Oxygenation as measured through Near Infrared Spectroscopy (NIRS) in individuals with MS.
4. A seven day moderate to high intensity water aerobics program will improve self-efficacy, as reported through the Multiple Sclerosis Self-Efficacy Scale in individuals with MS.

5. A seven day moderate to high intensity water aerobics program will not alter body composition, measured with Body Mass Index (BMI), Waist to Hip Ratio (WHR), and waist in individuals with MS.
CHAPTER II
REVIEW OF LITERATURE

Prevalence and Risk Factors for MS

Multiple Sclerosis (MS) is an autoimmune, demyelinating disorder of the central nervous system (Teusnissen, Dijkstra, & Polman, 2005). Worldwide, 1-2.5 million individuals suffer from Multiple Sclerosis (Doring, Pfueller, Paul, & Dorr, 2012; Anthony, Jouria, & Houtman, 2014). Multiple Sclerosis is the most common neurologic disorder in young adults (Teusnissen, Dijkstra, & Polman, 2005). In the United States there is a 0.1% instance in the general population (Anthony, Jouria, & Houtman, 2014) with diagnosis typically between the ages of 20-50 years (Kargarfard, Etemadifar, Baker, Mehrabi, & Hayatbakhsh, 2012).

There are multiple risk factors involved in MS. Women are 1.5 times more likely to have Multiple Sclerosis than men (Teusnissen, Dijkstra, & Polman, 2005), and women are twice as likely to be affected earlier in life (Kargarfard, Etemadifar, Baker, Mehrabi, & Hayatbakhsh, 2012). Inactivation and imprinting of the X chromosome causing a maternal parent-of-origin effect may be responsible for the increasing instance of females diagnosed with MS compared to males (Huynh & Casaccia, 2013). There is a geographical component to the disease with increased prevalence north of the equator, in industrialized countries, and in areas with less sunlight exposure (vitamin D deficiency) (Marrie, 2004; Ascherio & Munger, 2007b). Additional risk factors include smoking,
exposure to infections (with chronic latency) at a young age, and genetic predispositions (Ascherio & Munger, 2007a; 2007b; “NINDS,” n.d.).

Prevalence varies between different ethnic groups, further suggesting a genetic component (Hanwell & Banwell, 2011). Caucasians are twice as likely to be diagnosed with MS as other ethnicities (Khan & Pallant, 2007). Genome-wide association studies have identified specific nucleotide polymorphisms in genes that determine the genetic risk of developing MS (Huynh & Casaccia, 2013). Environmental factors may modify the epigenome and manifest as MS (Huynh & Casaccia, 2013). While there is no cure for Multiple Sclerosis, the disease course does not alter life expectancy (Anthony, Jouria, & Houtman, 2014).

**Signs and Symptoms of MS**

The primary symptoms of MS result from demyelination that occurs within the central nervous system (Anthony, Jouria, & Houtman, 2014). These symptoms include fatigue, heat sensitivity, muscle spasms, gait problems and ataxia, dizziness, pain, cognitive changes, visual complaints, bowel or bladder dysfunction (Anthony, Jouria, & Houtman, 2014). The great variation in symptoms (Table 1) and functional impact are a result of heterogeneity in the size and location of the focal lesions and the type of MS that is diagnosed.
Table 1

Prevalence of MS Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Prevalence</th>
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<tr>
<td>Fatigue</td>
<td>75-95%</td>
</tr>
<tr>
<td>Heat Sensitivity (Uhthoff phenomenon)</td>
<td>60-80%</td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td>80% experience some spasticity 15% experience painful muscle spasms (Foley et al., 2013; Brola, Mitosek-Szewczyk, &amp; Opara, 2014)</td>
</tr>
<tr>
<td>Decreased Physical Activity</td>
<td>80% of people with MS do not meet recommended moderate-to-vigorous physical activity levels (Molt, 2014)</td>
</tr>
<tr>
<td>Gait Problems</td>
<td>85% report gait disturbance as main complaint (van den Berg et al., 2006) and an estimated 40% will need walking assistance within 15 years of disease onset (Tyler et al., 2014)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>49-59% (Marrie, Cutter, &amp; Tyry, 2013)</td>
</tr>
<tr>
<td>Pain</td>
<td>29-86% (Brola, Mitosek-Szewczyk, &amp; Opara, 2014)</td>
</tr>
<tr>
<td>Visual problems</td>
<td>80% (Frohman, 2008)</td>
</tr>
<tr>
<td>Cognitive problems</td>
<td>40-70% (Frohman, et al., 2011)</td>
</tr>
<tr>
<td>Depression</td>
<td>50% (Feinstein, 2011)</td>
</tr>
<tr>
<td>Bowel or bladder dysfunction</td>
<td>80% (“Bladder Problems,” n.d.)</td>
</tr>
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**Fatigue**

Excessive fatigue, present in 75-95% of cases, is the most common disabling symptom of Multiple Sclerosis (Hugos et al., 2010; Cakit et al., 2010). Fatigue in MS is defined as abnormal sense of tiredness or lack of energy disproportional to the degree of effort or level of disability that significantly interferes with routine functioning and physical activity (Cakit et al., 2010). In 1/3 of MS individuals, fatigue is the only presenting symptom (Kargarfard, Etemadifar, Baker, Mehrabi, & Hayatbakhsh, 2012).
Fatigue and reduced exercise tolerance in MS is caused by central and peripheral factors that are involved in pathogenesis (Rampello et al., 2007). Central factors that cause fatigue include impaired voluntary drive of descending motor pathways, the inability to sustain central drive to spinal motor neurons, metabolic abnormalities in the frontal cortex and basal ganglia, and pro-inflammatory cytokines in the central nervous system (Comi, Leocani, Rossi, & Colombo, 2001). Peripheral fatigue factors commonly relate to deconditioning and include loss of force generating capacity in the muscle itself, decreased potentials in the motor unit, metabolic changes in the muscle, lower maximal voluntary force, lower muscle tension, longer relaxation time between repeated contractions, and slowed enzymatic re-synthesis required for energy synthesis (Comi, Leocani, Rossi, & Colombo, 2001).

Fatigue does not correlate with the degree of neurologic impairment or disability in MS (Klefbeck & Hamrah, 2003), and is differentiated as primary or secondary fatigue. Primary fatigue occurs as a result of the demyelination and axonal degeneration resulting from the disease process of the neuromuscular system in Multiple Sclerosis (Herbert, Corboy, Manago, & Schenkman, 2011). Secondary fatigue is caused by indirect factors such as depression, physical inactivity, or sleep disorder (Herbert, Corboy, Manago, & Schenkman, 2011). The presence of fatigue makes physical activity in this population challenging. In addition, recent studies conflict in regards to the benefits of exercise specifically on fatigue (Herbert, Corboy, Manago, & Schenkman, 2011; Yu, Billberg, Dalgas, & Stenager, 2013).
Fatigue may be a result of elevated muscle tone, respiratory muscle weakness, or the increased energy cost of ambulation found in MS individuals (Mostert & Kesselring, 2002). The inefficient gait patterns in MS reduce exercise tolerance and increase the metabolic cost of walking (Olgiati, Jacquet, & Di Prampero, 1986). MS individuals were found to have decreased limb endurance and impaired cardiorespiratory responses that were likely linked to deconditioning, autonomic dysfunction and altered breathing control (Chetta et al., 2004).

Yu and colleagues (2013) explored the relationship between primary fatigue and autonomic dysfunction and found that during cognitive and physical tasks, people with MS had a different autonomic response compared to healthy individuals. The vagus nerve was implicated through measuring decreased vagal tone, abnormal heart rate response, and abnormal heart rate variability (Yu, Billberg, Dalgas, & Stenager, 2013). The authors concluded that primary fatigue was linked to autonomic dysfunction. It was hypothesized that MS individuals mentally tire because the autonomic system fails to adjust important body functions which eventually result in autonomic nervous system failure (Yu, Billberg, Dalgas, & Stenager, 2013). In addition, body temperature is controlled by autonomic regulation, and fatigued individuals may have an abnormal response resulting in heat sensitivity, called the Uhthoff phenomenon (Yu, Billberg, Dalgas, & Stenager, 2013).

Fatigue affects quality of life and general functioning, and often leads to a downward spiral of inactivity and function. Diminished social relationships, affected
mental health, impaired activities of daily living and job loss are associated with fatigue in MS (Kargarfard, Etemadifar, Baker, Mehrabi, & Hayatbakhsh, 2012).

**Heat Sensitivity**

In 1890, William Uhthoff first described a temporary worsening of vision with exercise in individuals with optic neuritis (Bol et al., 2012). Later, symptoms were linked to hyperthermia (Bol et al., 2012). Uhthoff Phenomenon is present in 60-80% of individuals with MS (Anthony, Jouria, & Houtman, 2014). This phenomenon is caused when nerve conduction becomes blocked to central pathways as core body temperature increases (Davis et al., 2008; Humm et al., 2004; Frohman et al., 2013). The increased temperature can affect propagation of action potentials and lengthen the refractory period, resulting in a predisposition to conduction block (Davis, Wilson, White, & Frohman, 2010). Because of the demyelination in MS individuals, the blocked conduction occurs at a lower temperature, resulting in both physical and cognitive symptoms including fatigue, gait problems, decreased memory retrieval and information processing speed (Anthony, Jouria, & Houtman, 2014; Davis 44). The increase in core temperature can be caused by fever, exercise, or hot environment (Anthony, Jouria, & Houtman, 2014).

Several studies have examined possible mechanisms for the Uhthoff phenomenon in MS. Bol and colleagues (2012) suggested that hyperthermia altered the level of serum calcium resulting in a blockade of ion channels, circulatory changes, heat shock proteins and unidentified humoral substances. In addition, increased body temperature in MS may induce molecular changes in T-lymphocytes that exaggerate the immune response (Bol et
Lesions in the thalamus and hypothalamus may result in thermoregulatory dysfunction (Bol et al., 2012; Davis, Wilson, White, & Frohman, 2010). Peripherally, sweat gland function can be impaired in MS individuals, though it appears that neural control of skin blood flow remains intact (Davis, Wilson, White, & Frohman, 2010). Furthermore, the risk of overheating is amplified by the fact that individuals with MS voluntarily restrict fluid consumption due to bladder dysfunction (Davis, Wilson, White, & Frohman, 2010). This increased risk of hyperthermia and subsequent nerve dysfunction has placed a negative connotation on exercise as treatment in the past, but current MS research shows that exercise is a vital treatment component with demonstrated benefits (Hayes, Gappmaier, & LaStayo, 2011).

**Muscle Spasms**

Muscle spasms are involuntary muscle contractions that clinically present as feelings of muscle tightness or severe pain and uncontrollable contractions of the muscles in the extremities (Walker, Hall, & Hurst, 1990). Spasticity is a result of an exaggerated stretch reflex leading to increased muscle tone (Trompetto et al., 2014). The muscle spindle is a receptor within the body of the muscle that is sensitive to lengthening or stretching of the muscle (Walker, Hall, & Hurst, 1990). The stretch reflex is a monosynaptic reflex that increases alpha motor neuron activity in response to the muscle spindle being stretched, causing the muscle to contract (McArdle & Katch, 2010). The contraction shortens the muscle, alleviating the stretch. The regulation of the muscle
length prevents over-stretching that could damage the muscle-tendon unit (McArdle & Katch, 2010).

In MS, central nervous system lesions can damage upper motor neurons, disrupting the balance between supraspinal inhibitory and excitatory inputs that lead to the disinhibition of the stretch reflex (Trompetto et al., 2014). The corticobulbar fibers are white matter tracts that originate in the cerebral cortex and send facilitatory impulses to the brain stem and cranial nerves (Trompetto et al., 2014). The ventromedial reticular formation of the brain stem receives these facilitatory impulses passing them to the dorsal reticulospinal white matter tract (Trompetto et al., 2014). The dorsal reticulospinal tract originates in the ventromedial reticular formation and passes inhibitory signals to the muscle spindles (Trompetto et al., 2014). When this signal is disrupted due to demyelination or lesion, inhibition does not occur and the muscle spindle becomes over activated and can cause muscle spasms (Trompetto et al., 2014).

In MS, spasticity typically occurs in the legs, though it can occur in the upper extremity and even the low back. Due to the disease process and symptoms, MS individuals are often less active than the general population, which can increase the prevalence of spasticity (Hayes, Gappmaier, & LaStayo, 2011; Trompetto et al., 2014). Spasticity can also result in response to pain, infection, fever, and bowel distention (Anthony, Jouria, & Houtman, 2014).
**Decreased Physical Activity**

Due to fatigue and overheating issues, MS individuals are generally less physically active than healthy individuals of similar age (Hayes, Gappmaier, & LaStayo, 2011). Latimer-Cheung and colleagues (2013) conducted a meta-analysis that compared physical activity patterns of Multiple Sclerosis individuals, those without MS and chronic diseased people and concluded that MS individuals showed the lowest amount of physical activity. Rietberg and colleagues (2014) found that MS individuals have significantly lower dynamic activity compared to healthy individuals, starting with lower activity levels in the morning, persisting into the afternoon and evening. This may stem from adopting a lifestyle that anticipates energy conservation strategies including reducing physical activity, decreased number of transitions (sitting to standing), decreased dynamic movements (walking), and increased static movements (sitting and lying) (Rietberg, van Wegen, Kollen, & Kwakkel, 2014; Comi, Leocani, Rossi, & Colombo, 2001).

In studies controlled for gender, MS individuals on average were found to be in the 10th percentile for fitness (Bjarnadottir, Konradsdottir, Reynisdottir, & Olasfsson, 2007). Decreased activity levels lead to decreased mobility, balance and an increased risk of falling (Hayes, Gappmaier, & LaStayo, 2011). Multiple Sclerosis symptoms, along with lack of confidence in one’s abilities to manage the symptoms, can lead to impaired functioning, decreased physical activity and compromised quality of life (Doring, Pfueller, Paul, Dorr, 2012). The cycle of inactivity also appears to stem from
impairments on muscle function, sensation, coordination, balance, and stress from the
diagnosis leading to further inactivity, deconditioning and further disability (Kuspinar,
Anderson, Teng, Asano, & Mayo, 2010).

Less active lifestyles in MS individuals often coincide with diminished leisure
activities, social contacts, and normal activities of daily living which have all been found
to be important for self-esteem and psychological well-being (Reitberg, Brooks,
Uitdehagg, & Kwakkel, 2011). Self-efficacy is the belief in one’s capabilities to organize
and execute on the course of action required to manage a prospective situation (Hugos et
al., 2010). Higher levels of self-efficacy are beneficial in accomplishing tasks of daily
living. In addition, the primary aim of rehabilitation and treatment is to increase activity
levels and independence of MS individuals (Langdon & Thompson, 1999).

**Gait Problems and Ataxia**

Individuals with MS often have gait, mobility and posture difficulties. Mobility
or the process of moving within the environment, changing and maintaining postures is
one of the most valued health functions, and greatly impacts activities of daily living
(Rossier & Wade, 2001). Gait abnormalities are a result of muscle weakness, spasticity,
loss of balance, sensory deficit, and fatigue (“NINDS,” n.d.). Demyelination causes
deficiencies in strength and coordination in balance (Reitberg, Brooks, Uitdehagg, &
Kwakkel, 2011). Muscle weakness can cause the toe to drag, foot drop, compensatory
hip hike, trunk lean, or swinging the leg out to one side during walking, all leading to
Frzovic and colleagues (2000) found MS individuals to perform worse on balance measures than healthy individuals. Gait speed and agility is often measured in MS through the dynamic gait index and timed walk tests (McConvey & Bennett, 2005). Slower ambulation speeds correlate to balance dysfunction assessed with the Berg Balance Scale (McConvey & Bennett, 2005). Sensory deficits such as severe numbness in the feet so that the individual cannot feel the floor or perceive the location of their feet often contribute to gait problems (“NINDS,” n.d.). To further complicate gait abnormalities, demyelination of the vestibular nerve or area around the vestibular nuclei in the brainstem causes dizziness, vision deficiencies, and balance problems (McConvey & Bennett, 2005).

Ataxia or loss of muscle coordination can affect speech, eye movements, swallowing, gait and picking up objects. Lesions in the cerebellum can cause cerebellar ataxia resulting in deficiencies in sensory perception, coordination and motor control. This presents as floppiness (hypotonia), lack of coordination, and the inability to control the distance, power and speed of an arm, leg or even eye movements (Anthony, Jouria, & Houtman, 2014). Nerve lesions and demyelination can also affect descending and ascending neural tracts within the central nervous system. Lesions in the vestibulocerebellar (vestibular nuclei – cerebellum) tracts cause balance and eye movement dysfunction, resulting in a wide foot stance in gait to compensate for poor balance (“medical news today,” n.d.). Spinocerebellar (spinal cord-cerebellum) lesions produce an unusual gait with unequal or sideways steps and uncertain stops and starts.
Cerebrocerebellar (cerebrum-cerebellum) tract lesions make voluntary planned movements difficult, and result in trembling and slurred speech ("medical news today," n.d.).

Gait problems and ataxia contribute to deconditioning in individuals with MS due to the abnormally high energy cost of walking, leg fatigue, respiratory muscle dysfunction and cardiovascular autonomic dysfunction (Rampello et al., 2007). Chetta and colleagues (2004) documented significantly lower oxygen pulse (VO$_2$/HR) and impaired breathing pattern during walking, and a significantly higher ventilatory equivalent of carbon dioxide at rest and walking. Gait is further limited by fatigue, fear of falling, sensory and motor deficits (van den Berg et al., 2006; Dibble, Lopez-Lennon, Lake, Hoffmeister & Gappmaier, 2013). Consequentially, MS individuals adapt their lifestyle to conserve energy, leading to further deconditioning and weakness (Marck et al., 2014). Multiple Sclerosis has also been found to impair gait speed, cadence, stride length and time spent on double limb support which correlates to reduced independence, productivity, and a negative impact on overall quality of life (Tyler et al., 2014; Asano & Finlayson, 2014).

**Dizziness**

Of MS individuals, 49-59% suffers from dizziness that can decrease mobility and quality of life (Marrie, Cutter, & Tyry, 2013). Although previously thought that lesions at the pons in the vestibulocochlear nerve (responsible for hearing, balance, and body position sense) caused demyelinating acute vestibular syndrome resulting in dizziness...
and vertigo in MS individuals, Pula and colleagues (2013) documented that lesions throughout the brainstem and cerebellar peduncles are also implicated in these symptoms.

Dizziness in MS is categorized as centrally caused acute vestibular syndrome (AVS) or peripherally caused positional vertigo. AVS is a single, elongated, spontaneous episode of acute vertigo that is coupled with nausea, vomiting, nystagmus, and gait disturbance (Pula, Newman-Toker, & Kattah, 2013). Mostly, AVS is caused by vestibular neuritis and stroke, with 10% resulting from demyelination (Pula, Newman-Toker, & Kattah, 2013). Active lesions near the fourth ventricle interrupt the otolithic projections in the superior cerebellar peduncle causing positional vertigo (Pula, Newman-Toker, & Kattah, 2013). Demyelination, lesions, and dysfunction in the brainstem, cerebellum, and the audiovestibular system lead to reduced ability to integrate multiple sensory inputs (Alpini, Caputo, Pugnetti, Giuliano, & Cesarani, 2001). The cerebellum and brainstem are linked to sensory input and motor output, and the audiovestibular system is involved in multisensory integration and coordination of motor responses (Alpini, Caputo, Pugnetti, Giuliano, & Cesarani, 2001). The result is dizziness, vertigo and gait imbalances.

**Pain**

Pain in MS rarely presents early in the disease process, but often increases with the progression of MS (Brola, Mitosek-Szewczyk, & Opara, 2014). Pain can influence the rehabilitation process and quality of life. Of those with pain, 40% experienced difficulty working, 44% had difficulty sleeping, and 34% had troubled interpersonal
relationships (Brola, Mitosek-Szewczyk,, & Opara, 2014). Central neuropathic pain is caused by damage to the nervous system due to the demyelination and axon damage caused by MS (Brola, Mitosek-Szewczyk, & Opara, 2014). Peripheral pain is infrequent in MS individuals.

Pain is typically classified as primary pain resulting from the disease process, and includes painful tonic spasms, Lhermitte’s sign, and trigeminal neuralgia and glossopharyngeal neuralgia (Anthony, Jouria, & Houtman, 2014; Brola, Mitosek-Szewczyk,, & Opara, 2014). Spasms caused by MS pathology can directly cause pain (Chetta et al., 2004). Lhermitte’s sign is a brief electrical shock-like sensation that runs down the spine and is triggered by bending the neck, and is considered a classic sign of MS (Anthony, Jouria, & Houtman, 2014). Trigeminal and glossopharyngeal neuralgia are caused by lesions to those cranial nerves and result in abrupt, sharp unilateral facial pain (Warren, Kotsenas, & Czervionke, 2006). Secondary pain, such as back pain, occurs as a result of already existing symptoms such as poor posture and gait (Brola, Mitosek-Szewczyk, & Opara, 2014).

Pain is also classified according to duration as acute or chronic. Acute or rapid onset of pain results from lesions in the pons, brainstem and the nerve itself and clinically manifests as attacks of burning pain in the extremities, spasmic pain, and Lhermittes sign. Chronic or long duration pain usually manifests as pain in the lower limb and back (Brola, Mitosek-Szewczyk, & Opara, 2014).
Current theory in MS associates pain with demyelination and damage to axons which alters the function of ion channels and results in hyper-excitability (Brola, Mitosek-Szewczyk, & Opara, 2014). Damage in the sensory tract projections in the thalamus and parietal cortex causes a hyper-excitability and results in referred pain. Pain has also been associated with lesions in the spinothamocortical pathways, increasing the interpretation of pain from the periphery to the thalamus and cortex (Brola, Mitosek-Szewczyk, & Opara, 2014).

**Visual Problems**

In MS, demyelination can occur in any part of the brain, and if damage occurs in the optic nerve or in the nerve tracts controlling eye movement, visual impairment can occur (McConvey & Bennett, 2005; Doring, Pfueller, Paul, Dorr, 2012). In about 20% of people with MS, retrobulbar optic neuritis is the first presenting symptom (Brola, Mitosek-Szewczyk, & Opara, 2014). Blurred vision, complete vision loss, color vision deficiency, decreased contrast sensitivity, blindness in one eye, and a dark spot in the center of the visual field are common symptoms (Brola, Mitosek-Szewczyk, & Opara, 2014; “Pain,” n.d.; Frohman, 2008). These symptoms are caused by an inflammation of the optic nerve or lesions along the nerve pathways controlling eye movement and visual coordination (“Pain,” n.d.). Symptoms typically subside 10-20 hours later, and 70-80% of MS individuals experiencing optic neuritis regain vision completely (Brola, Mitosek-Szewczyk, & Opara, 2014). Nystagmus, or uncontrolled horizontal or vertical eye movement can also occur in MS (“Pain,” n.d.). Diplopia or double vision is a result of
weakness in the eye muscles that control eye movement. The weakness causes uncoordinated movements, resulting from the fact that the visual image is not being properly fused (“Pain,” n.d.).

**Cognitive Changes**

40-70% of individuals with MS experience cognitive impairment (Frohman et al., 2011). Cognitive decline in MS is due to functional disconnections of different cortical areas; in addition, individuals with MS display a smaller mean brain volume than healthy individuals (Filippi et al., 2000). In fact, deterioration of gray matter and white matter structures in cortical tissue is associated with functional and cognitive limitations (Prakash, Snook, Motl, & Kramer, 2010).

Cognitive changes can include diminished concentration or memory retrieval, deficits in executive functioning, and slowed information processing (Anthony, Jouria, & Houtman, 2014). In addition, deficits in abstract reasoning, problem solving, visuospatial skills are common in MS individuals (Amann et al., 2011). Multiple Sclerosis patients usually retain the ability to consolidate new memories and rarely exhibit dementia (Anthony, Jouria, & Houtman, 2014). Kavcic and Scheids (2011) suggested the mechanisms for attentional deficits were due to unreliable inhibitory processes that depend on white matter connections between early perceptual models and working memory models. Demyelination of these circuits slows conduction and information processing (Kavcic & Scheid, 2011).
Several imaging studies have proposed that early in the disease process, the brain adapts and compensates for potential cognitive deficits before clinical symptoms are revealed (Amann et al., 2011). Multiple areas of the brain in MS individuals have presented greater activation compared to healthy controls (Amann et al., 2011). Audan and colleagues (2003) reported greater activation, as measured with functional magnetic resonance imaging (fMRI), in the right prefrontal cortex, right and left lateral frontal cortex, and right cerebellum in MS individuals during the administration of paced auditory serial addition test (PASAT). The PASAT is an established test that assesses sustained attention, speed of information processing and working memory (Forn et al., 2006). Forn and colleagues (2006) also showed greater activation (fMRI) of the left, middle, and inferior frontal cortex, even though MS individuals did not perform worse on the tasks than healthy individuals. Through alertness tasks, Penner and colleagues (2003) demonstrated increased activation in the right dorsolateral frontal cortex, right lateral cerebellum, right superior temporal gyrus, left angular gyrus, and left and right inferior parietal cortex. Assessing working memory through comparison of the auditory 2-back task versus 0-back task resulted in preserved performance in MS compared to healthy individuals, but the MS individuals had greater fMRI activation in the prefrontal cortex and the insula (Forn et al., 2007). Amann and colleagues (2011) compared RRMS individuals that did not exhibit signs of cognitive decline with healthy controls. Functional maps showed that RRMS had a greater brain activation shown on fMRI with simple tasks and there was a saturation effect of (de)activation at the highest task load.
Differences were found in the right parahippocampal cortex, and the medial and middle frontal regions (Amann et al., 2011).

As a result of the demyelinating events, deficits in conscious perception and higher order cognitive functions can have a high impact on daily functions. In MS individuals, brain activation patterns and functional adaptation patterns change before the cognitive impairments manifest clinically (Amann et al., 2011). The mechanism for changed activation patterns is thought to be an enlargement of neuron cell bodies that expand dendritic arborization and post synaptic structures which compensates disruptions in neuronal connectivity lesions (Amann et al., 2011). It is also possible that damaged circuits induce alternative networks to become functional (Amann et al., 2011).

Weak correlations between demyelinating lesions and neurologic disability point to a pathophysiology outside of the white matter lesions (Prakash, Snook, Motl, & Kramer, 2010). Filippi and colleagues found that normal appearing brain tissue undergoes changes including increased number of astrocytes, patchy edema, perivascular cellular infiltration, and abnormally thin myelin and axonal damage that significantly contribute to the clinical symptoms of MS, but go undetected by current imaging technology (Filippi et al., 2000; Cohen-Adad et al., 2011).

Depression

Thirteen to thirty percent of individuals with MS suffer from major depressive disorder with a lifetime risk of up to 50% (Fischer, Heesen, & Gold, 2011). Depression can interfere with treatment compliance, is associated with cognitive impairment, and
appears to be underdiagnosed and undertreated in the MS population (Huynh & Casaccia, 2013). Depression can decrease quality of life, can lead to suicidal intent or suicide, and can impair relationships (Feinstein, 2011). Depression in MS is not correlated to severity of neurological impairment and can occur at any stage of the disease process (Huynh & Casaccia, 2013; Feinstein, 2011). Typical symptoms include insomnia, early morning awakening, loss of appetite, loss of concentration, fatigue, and short-term memory deficits (Anthony, Jouria, & Houtman, 2014).

It is thought that depression in MS is caused by hyperactivity of the hypothalamic-pituitary-adrenal axis, stress and excess glucocorticoid levels, inflammation, disturbed energy homeostasis and abnormal evening (but normal morning) cortisol levels (Fischer, Heesen, & Gold, 2011). Neuroimaging studies have documented structural brain changes, such as greater lesion load, less gray matter volume and increased cerebrospinal fluid volume in the left anterior temporal region, that explain 42% of the variance in major depression in this group (Feinstein, 2011). Psychosocial and disease related factors including emotional based coping, uncertainty, loss of hope, and degree of physical disability accounted for 40% of the variability causing major depression in MS individuals (Feinstein, 2011). Genetics has not been connected to depression in MS (Feinstein, 2011). As individuals progress in MS symptoms such as impairments in gait, balance, and sensation, their levels of self-efficacy diminish and depression often increases.
Bowel and Bladder Dysfunction

Spastic bladder dysfunction occurs in 80% of MS individuals and is characterized by the inability to hold the normal amount of urine or the inability to empty the bladder properly (“Bladder Problems,” n.d.). Cervical cord lesions in MS individuals have been correlated to the inability to hold the normal volume of urine, whereas, improper bladder emptying has been associated with brainstem and pontine lesions (Frohman, et al., 2011). MS lesions block or delay the transmission of nerve signals in the central nervous system that control bladder and urinary sphincters (“Bladder Problems,” n.d.). The results are frequency and urgency of urination, hesitation at the start of urination, frequent nighttime urination (nocturia), incontinence (the inability to hold urine), and the inability to empty the bladder completely (“Bladder Problems,” n.d.). Complications that arise when bladder dysfunction is untreated include worsening of symptoms, repeated urinary tract infections and kidney stones, challenges at home and work, and loss of independence, self-esteem and self-confidence (“Bladder Problems,” n.d.).

Bowel dysfunction includes constipation and fecal incontinence (Frohman, et al., 2011; “Bowel Problems,” n.d.). Both can lead to discomfort and humiliation, and constipation can further aggravate spasticity and bladder dysfunction (“Bowel Problems,” n.d.). Causes can include insufficient fluid intake, decreased physical activity and mobility, slowed motility through the digestive tract, and side effect of medications in treatment of MS symptoms (“Bowel Problems,” n.d.).
MS Pathology

Symptoms in MS result from three forms of pathology: demyelination of axons, focal plaques, and inflammation. It is uncertain if inflammation is the primary pathogenic event, if neurodegeneration occurs first, or if inflammation and neurodegeneration act in tandem or independently (Compston & Coles, 2008). Axons in the central nervous system are myelinated by cells called oligodendrocytes. An oligodendrocyte will contact 20-40 short segments of axons that are adjacent to each other. The oligodendrocyte wraps around the axons, forming a myelin sheath that is separated by nodes of Ranvier. Growth factors, including brain derived neurotropic factor, regulate the production, migration, and maturing of oligodendrocytes (Compston & Coles, 2008). During the myelination process, mature sodium channels are retained along the axon while low electrical resistance sodium channels develop within the nodes of Ranvier facilitating depolarization and allow for the saltatory conduction of the electrical signal (Compston & Coles, 2008). However, when the myelin sheath is broken down, impulse conduction is compromised, as seen in MS.

Early in the disease process, oligodendrocytes are able to re-myelinate the axons and restore functional nerve transmission (Compston & Coles, 2008). The inflammatory response subsides and the clinical symptoms diminish. Initially in the disease process, approximately 85% of MS individuals experience neurological relapse followed by periods of remission (Hauser & Oksenberg, 2006). However, over time reoccurring attacks on the myelin sheath translate to permanent damage in which re-myelination does
not occur and symptoms progress. The irreversible changes result in gliosis (scarring),
axonal damage, neuronal degeneration and cerebral atrophy (Anthony, Jouria, &
Houtman, 2014). Loss of myelin slows nerve transmission resulting in decreased sensory
sensitivity, hyper-reflexia and muscle spasm (Compston & Coles, 2008).

Demyelination can occur through multiple mechanisms. Programmed cell death
of oligodendrocytes, and hyperactivity of astrocytes results in scarring of permanent
tissue and subsequent destruction to the myelin, prevention of remyelination and causing
permanent damage (Teusnissen, Dijkstra, & Polman, 2005; Waid et al., 2014). Antibody-
mediated demyelination results from T lymphocytes that are auto-reactive for myelin
proteins (Teusnissen, Dijkstra, & Polman, 2005; Berger et al., 2003; Anthony, Jouria, &
Houtman, 2014). The auto-activated T lymphocytes breach the blood brain barrier and
attack neurons of the central nervous system (Compston & Coles, 2008). Although the
triggers for this breach are unknown, it has been suggested that intracellular adhesion
molecules, specifically ICAM-1, located on the vascular endothelium of the brain and
spinal cord increase their permeability to these activated lymphocytes (Anthony, Jouria,
& Houtman, 2014). Lymphocytes then recruit myelin-based antigens along with
cytokines that are activated by microglial cells causing the inflammatory response
(Anthony, Jouria, & Houtman, 2014; Compston & Coles, 2008). Microglial cells
typically phagocytize debris and foreign materials, but when activated they can enhance
the inflammatory phase by producing pro-inflammatory cytokines and reactive oxygen
species (Frohman, O’Donoghue, & Northrop, 2011). An inflammatory cascade including
the release of cytokines that promote expression of class II major histocompatibility complex (MHC) molecules, nitric oxide, free radicals, and superoxide which amplify the inflammatory response, leading to destruction of the myelin sheath (Anthony, Jouria, & Houtman, 2014).

In healthy individuals, inflammation promotes wound healing and signals angiogenesis, neuroprotection, and maintenance of the tissues (Hauser & Oksenberg, 2006). However in MS individuals, the inflammatory process becomes excessive, causing damage to the neuronal structures. Class II MHC molecules, only found on antigen presenting cells, phagocytize foreign material, digest it and then present pieces of the foreign pathogen on its own cell membrane in order to alert immune system cells of the foreign presence. However, the pathogen has enough structurally in common with body cells to cause a misguided response targeting cells that belong to the body resulting in an autoimmune inflammatory attack on the myelin sheath. When an autoimmune response mounts, there is a loss of control over the immune system, and an activation of lymphocytes that destroy the myelin sheath, trigger inflammation, and cause axonal damage (Hauser & Oksenberg, 2006).

Focal plaques are also involved in the pathogenesis of MS. A plaque is the end stage of inflammation and demyelination, caused by oligodendrocyte depletion, astrocytosis (an increase in the number of astrocytes which work to repair the damaged tissue by laying down scar tissue) and neuronal and axon degeneration (Compston & Coles, 2008). Focal plaques, or local zones of injury, cluster around the lateral ventricles,
corpus callosum, in the cortex and sub cortical white matter, optic nerves, brainstem and spinal cord (Compston & Coles, 2008). The variability in location of focal lesions and extent of axon damage contributes to the heterogeneity of the disease process among individuals with Multiple Sclerosis (Anthony, Jouria, & Houtman, 2014; Mostert & Kesselring, 2002; Waid et al., 2014). Six out of seven lesions detected by MRI are clinically silent, however, high lesion load in MS individuals early in the disease process is correlated to greater risk of disability in later disease stages (Hauser & Oksenberg, 2006; Sun, Tanaka, Kondo, Okamoto, & Hirai, 1998).

In MS, mostly white matter is affected, but gray matter damage can also be detected (Waid et al., 2014). Cortical plaques produce motor, sensory and cognitive symptoms, and microglia activation has been correlated to lesions in the cortex (Hauser & Oksenberg, 2006). T2*-MRI is more sensitive to cortical lesions and has shown a correlation between EDSS (Expanded Disability Status Scale) indicating disability and lesions in the primary motor cortex (Cohen-Adad et al., 2011). White matter plaques are associated with increased number of lymphocytes that are able to cross the blood brain barrier (Hauser & Oksenberg, 2006). Tissue damage undetected by MRI extends beyond the focal plaque into normal appearing white matter and normal appearing gray matter (Ge et al., 2009, Prakash, 41, Cohen-Adad et al., 2011).

In addition to the three types of pathology reviewed above, MS can also result in hypometabolic changes to the brain including decreased oxygen utilization, brain vascular changes, and mitochondrial damage (Ge et al., 2009). The healthy brain
consumes a significant amount of the body’s total energy, about 20%, through aerobic metabolism (Gallagher et al., 1998). However, in MS individuals, prior studies have shown a reduced absolute cerebral blood flow and cerebral oxygen metabolism in gray and white matter (Sun, Tanaka, Kondo, Okamoto, & Hirai, 1998; Brooks et al., 1984). Ge and colleagues found a diminished global oxygen extraction fraction (OEF) in MS compared to healthy individuals that correlated to disability and lesion volume (Ge et al., 2009). OEF is the percent of oxygen that is removed from the bloodstream by the tissues during its passage through the capillary network, and it demonstrates uniformity even with regional variations in cerebral blood flow and cerebral metabolic rate (He, Zhu, & Yablonskiy, 2008). This uniformity suggests that an established equilibrium exists between local metabolic requirements needed for neuronal activity and the level of blood flow to that local area (He, Zhu, & Yablonskiy, 2008). Neuronal activation is associated with quick vasodilation that increases oxygen uptake in order to meet the increasing metabolic needs (Lintas, Molinari, Simonetti, Franzini, & Liboni, 2013).

Measuring deoxyhemoglobin gives a regional metabolic picture which is important because metabolic disturbances could relate to lesion formation and inflammation near cortical veins, as well as cognitive decline (Kidd et al., 1999). Fan and colleagues (2015) demonstrated that while OEF (through MRI) did not correlate to measures of structural damage, OEF did correlate with cognitive measures, specifically with information processing speed. These authors suggested that cerebral oxygenation may be sensitive to pathologic processes that are different from those detected by MRI.
MRI may not be sensitive enough to detect structural changes that happen independently or in conjunction with hemodynamic changes that could contribute to the pathology of MS (Bakshi, Miletich, Kinkel, Emmet, & Kinkel, 1998; Fan et al., 2015; Kidd et al., 1999).

Positron emission tomography (PET) examination revealed a decreased brain oxygen utilization and extraction present in MS accompanied by extensive reduction in cerebral glucose metabolism (Brooks and colleagues, 1984). Bakshi and colleagues, (PET scan) demonstrated hypometabolic activity in the cerebral cortex, subcortical nuclei, supratentorial white matter, and infratentorial structures (Bakshi, Miletich, Kinkel, Emmet, & Kinkel, 1998). Sun and colleagues (1998) found that as disability increased, oxygen metabolism decreased, which was also correlated with cognitive impairment. The level of cerebral hypometabolism was also correlated to the number of relapses.

Sun and colleagues (1998) suggest that white matter lesions may cause cerebral hypometabolism that is responsible for clinical disability. The axonal transport breakdown may exert a depressant effect on the cerebral cortex (Sun, Tanaka, Kondo, Okamoto, & Hirai, 1998). Brooks and colleagues (1984) propose that the decrease in oxygen utilization is likely due to non-exchanging tissue that develops from cerebral atrophy rather than decreases in oxygen utilization from intact neurons. They also suggest that the hypometabolism may result from submicroscopic plaques that lead to Wallerian degeneration, or suppression of neuronal activity by a toxin produced from the
myelin breakdown. Brooks and colleagues (1984) also found cognitive impairment to correlate with cerebral atrophy and levels of cerebral oxygen utilization.

MS is recognized as a diffuse global brain pathology that has a major vascular impact (Ge et al., 2009). During normal functioning, metabolic gas exchange at the brain capillary level extracts oxygen from hemoglobin resulting in deoxyhemoglobin with four unpaired electrons (Ge et al., 2009). In MS individuals, the oxygen extraction is diminished which also reduces deoxyhemoglobin that is detected in the venous network (Ge et al., 2009). In addition to reduced oxygen to the brain tissues, Ge and colleagues (2009) also found cerebral chronic venous insufficiency in MS individuals with venous visibility negatively correlated to lesion load. Widespread decreases in brain venous blood oxygenation levels reflect the cerebral hypometabolic picture in MS (Ge et al., 2009). Ge and colleagues (2009) found decreased visibility of periventricular white matter venous vasculature in MS subjects when compared to healthy controls. The proposed mechanism is two-fold: a decrease in oxygen utilization in tissue and a decrease in glucose utilization in cortico-cerebral metabolism that is correlated with lesion load (Ge et al., 2009; Blinkenberg et al., 2000).

Witte and colleagues (2009) studied the impact of MS on mitochondria and found that demyelination increases the energy requirement of neurons. The impaired conduction is compensated for by increasing the sodium channels and sodium potassium pumps along the axon, which require ATP to function (Witte et al., 2009). The number of mitochondrion increase in an attempt to provide for the increased energy need as
demonstrated by the increased density in astrocytes and axons of MS lesions (Witte et al., 2009). A byproduct of the mitochondria is intracellular reactive oxygen species (ROS) which cause damage to the mitochondrial DNA, mitochondrial proteins, and possibly further increasing neuronal degeneration (Witte et al., 2009).

Lintas and colleagues (2013) used Near Infared Spectroscopy System (NIRS) to monitor oxygenated and deoxygenated hemoglobin and Cytochrome-c-oxidase, an enzyme in the mitochondria. Mitochondrial damage, characteristic to MS, is reflected by lower levels of cytochrome-C-oxidase in MS individuals compared to healthy controls (Lintas, Molinari, Simonetti, Franzini, & Liboni, 2013). The oxidative damage to DNA induced by inflammation in chronically active plaques is a proposed mechanism to the diminished metabolic capacity of brain tissue in MS (Lintas, Molinari, Simonetti, Franzini, & Liboni, 2013). Fischer and colleagues (2013) found that 80% of the gene expression changes that are MS specific are related to the following interconnected molecular pathways: inflammation, oxidative stress associated with DNA damage that leads to mitochondrial damage, and regeneration mechanisms that affect oligodendrocytes, neurons, and neuronal cell processes.

**Types of MS**

Multiple Sclerosis often starts with a neurological episode in which the symptoms can be unifocal or multifocal. When one sign or symptom presents, it is termed unifocal, and is caused by a single lesion; for example, optic neuritis (“Clinically Isolated Syndrome,” n.d.). Multifocal symptoms are multiple symptoms that result from lesions
located in more than one location ("Clinically Isolated Syndrome," n.d.). The first episode an individual sustains is termed Clinically Isolated Syndrome and treatment focuses on delaying the conversion into MS (Anthony, Jouria, & Houtman, 2014; “Clinically Isolated Syndrome,” n.d.).

Benign Multiple Sclerosis remains dormant after the Clinically Isolated Syndrome with a long term absence of symptoms of greater than 10 years. Leray and colleagues (2013) completed a 30 year observational study and found that one-third to one-half of individuals diagnosed with clinically definite benign MS with no disability at 10 years after disease onset developed disability over a 30 year period. However, once the individual experiences further neurological episodes, and a MS diagnosis is made, classification of Multiple Sclerosis is characterized by specific onset and symptoms.

The major forms of MS include: Relapsing Remitting MS (RRMS), Secondary Progressive MS (SPMS), Primary Progressive MS (PPMS), and Malignant MS (Marburg’s variant). Relapsing Remitting (RRMS) is the most common form of MS, accounting for 85% of Multiple Sclerosis cases (“Types of MS,” n.d.; Berger et al., 2003). RRMS is characterized by exacerbations followed by periods of remission, and is attributed to demyelinating attacks followed by remyelination by the oligodendrocyte (Goldenberg, 2012). RRMS often develops into secondary progressive multiple sclerosis (SPMS) in people who have been diagnosed with RRMS for at least 10 years (“Types of MS,” n.d.). Secondary progressive MS is characterized by neurologic impairment between relapses without any remission period, as evidenced through clinical symptoms.
The individual continues through progressive deterioration and incomplete recovery from each relapse (Lublin & Reingold, 1996). Primary progressive multiple sclerosis (PPMS) accounts for 10% of MS cases (Koch, Kingwell, Riekmann, & Tremlett, 2009). PPMS is distinguished by steady disease progression interspersed with occasional remission involving temporary mild improvements, and this form has more lesions in the spinal cord than in the brain with greater effects on mobility (Lublin & Reingold, 1996; Antel, Antel, Caramanos, Arnold, & Kuhlmann, 2012). There is a lower inflammatory response linked with less brain lesions and fewer inflammatory cells in PPMS than RRMS (Antel, Antel, Caramanos, Arnold, & Kuhlmann, 2012). In addition, men and women are affected equally (Antel, Antel, Caramanos, Arnold, & Kuhlmann, 2012). Compromise of oligodendrocytes and myelin repair are greater in this type of MS (Anthony, Jouria, & Houtman, 2014).

A hallmark of MS is chronic intrathecal production of immunoglobulin, specifically oligoclonal IgG (Gurkov, 2005). In 90% of PPMS cases there are increased intrathecal IgG antibodies and oligoclonal bands in the cerebral spinal fluid (Gurkov, 2005; Puccionin-Sohler, 1995; Haertle, Kallweit, Weller, & Linnebank, 2014). Oligoclonal bands are proteins called immunoglobulins, and their presence indicates inflammation in the CNS (Haertle, Kallweit, Weller, & Linnebank, 2014). The increase in oligoclonal bands is a result of an immune reaction that causes antibody synthesis from B Lymphocytes that have infiltrated the perivascular region (Haertle, Kallweit, Weller, & Linnebank, 2014). A systemic immune reaction does not have to be present with an
increase in oligoclonal bands, and is common in MS due to autoimmune inflammation (Haertle, Kallweit, Weller, & Linnebank, 2014).

A more severe but rare (5%) case, progressive-relapsing (PRMS) has high mortality rates (Lublin & Reingold, 1996; Goldberg, 2012). Steady progression of neurological damage with acute exacerbations, absent of total remission leads to progressive permanent decline (Anthony, Jouria, & Houtman, 2014). Malignant MS (Marburg’s variant) is a rapidly progressive form with major disability, and death within one year. Children are more commonly affected but it can be found in older adults as well (Anthony, Jouria, & Houtman, 2014).

**Standard Treatment of MS**

Table 2

*Standard Treatment of MS*

<table>
<thead>
<tr>
<th>Indication</th>
<th>Drug</th>
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<tbody>
<tr>
<td>Acute Exacerbation, Shorten Duration of Attack</td>
<td>Corticosteroids: methylprednisolone or dexamethasone</td>
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<td></td>
<td>Adrenocorticotropic Hormone</td>
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<td></td>
<td>Immunosuppressive drugs (i.e.: cyclophosphamide,</td>
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<td></td>
<td>methotrexate, azathioprine, cyclosporine)</td>
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<tr>
<td>Reduce Disease Activity and Progression</td>
<td>Immunomodulatory</td>
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<td></td>
<td>β interferons</td>
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<td></td>
<td>Glatiramer acetate</td>
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<td></td>
<td>Immunosuppressive</td>
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<td></td>
<td>Mitoxantrone</td>
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<td></td>
<td>Natalizumab</td>
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<td></td>
<td>Fingolimon</td>
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<td></td>
<td>Dimethyl Fumarate</td>
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<td>Symptomatic Therapy</td>
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<td>------------------------------------------</td>
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<tr>
<td>Fatigue</td>
<td>Amantadine or Modafinil</td>
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<tr>
<td>Heat Sensitivity</td>
<td>Potassium Channel Blockers</td>
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<tr>
<td>Spasticity</td>
<td>Sodium Channel Blockers</td>
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<td></td>
<td>Baclofen</td>
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<td></td>
<td>Tizanidine</td>
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<td></td>
<td>Benzodiazepines</td>
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<tr>
<td>Gait Problems</td>
<td>Ampyra</td>
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<tr>
<td>Dizziness, Vertigo</td>
<td>Anti-motion sickness medications (Meclizine, Scopolamine)</td>
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<td></td>
<td>Anti-nausea (Ondansetron)</td>
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<td>Pain</td>
<td>Corticosteroids</td>
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<td>Antiepileptic medications</td>
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<td>Tricyclic antidepressants</td>
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<td>Lidocaine</td>
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<td>Mexiletine</td>
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<td>Vision</td>
<td>Non-steroidal anti-inflammatory medications</td>
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<td></td>
<td>Corticosteroids (for optic neuritis pain)</td>
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<td></td>
<td>Methylprednisolone, prednisone</td>
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<td></td>
<td>Baclofen (for nystagmus)</td>
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<td></td>
<td>Antiseizure medications and surgical techniques (trigeminal neuralgia, glossopharyngeal neuralgia)</td>
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<td>Cognitive Problems</td>
<td>Amphetamines (cognitive performance)</td>
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<td>Acetylcholinesterases (working memory)</td>
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<td>Depression</td>
<td>Tricyclic antidepressants (amitriptyline, serotonin reuptake inhibitors)</td>
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<td>Bowel and Bladder Dysfunction</td>
<td>Antimuscarinics, anticholinergics (bladder dysfunction)</td>
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<td>Tricyclic antidepressants (bladder incontinence)</td>
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<td></td>
<td>Desmopressin (nocturia)</td>
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<td></td>
<td>Stool softeners, suppositories, enemas (constipation)</td>
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<td></td>
<td>Loperamide (fecal incontinence)</td>
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For individuals with mild MS without relapses, no treatment is required. In more progressive MS, treatment strategies target acute exacerbations, reduce the disease activity and progression, and treat the symptoms of MS (Table 2). When individuals have acute exacerbations, treatment often includes corticosteroids and adrenocorticotropic hormone (ACTH) (Goodin et al., 2002). These pharmacological treatments promote quicker resolution of neurological deficits, lower the severity of the attack while also reducing the risk of permanent deficits. These drugs also help to restore the blood brain barrier, reduce inflammation, and work through immunomodulating trafficking mechanisms (Arnason, Berkovich, Catania, Lisak, & Zaidi, 2013, Anthony, Jouria, & Houtman, 2014). Corticosteroids and ACTH are able to block the adhesion and migration of mononuclear phagocytes through the blood brain barrier, preventing their movement or trafficking into the central nervous system (Anthony, Jouria, & Houtman, 2014). It is not advantageous to take corticosteroids or ACTH long term, and they serve as acute exacerbation treatments (Goodin et al., 2002). Immunosuppressive drugs can also be prescribed for acute exacerbations; however they increase susceptibility to infection (Anthony, Jouria, & Houtman, 2014).

Immunomodulation drugs are used to slow the disease progression and reduce the disease activity. These drugs can help to reduce the relapse rate and progression of RRMS possibly by activating impaired immune cells and decreasing blood brain barrier permeability (Goldenberg, 2012; Anthony, Jouria, & Houtman, 2014). The most frequently prescribed immunomodulators are beta(β)-interferons which decrease acute
exacerbations in MS by 30% and reduce the risk of new lesion formation by 70-90%, and reduce the severity of attacks (Goodin et al., 2002; Rejdak, Jackson, & Giavonnoni, 2010). Beta interferon reduces the rate of disease progression by twelve months in the short term (Rejdak, Jackson, & Giavonnoni, 2010).

Glatiramer acetate is believed to block myelin-damaging T-cells and increase the number of immune regulatory cells that suppress the immune response resulting in reduced inflammation (Goldenberg, 2012). Glatiramer acetate also decreases relapse rate by 1/3 (Rejdak, Jackson, & Giavonnoni, 2010).

Mitoxantrone is a cytostatic (cell stopping) drug that is used to treat RRMS and progressive forms of MS. Its anti-inflammatory effect helps to resolve relapses, however there is high risk for leukemia and cardio-toxicity and is only used in treating advanced MS (Goldenberg, 2012; Goodin et al., 2002). Mitoxantrone suppresses T and B cells, and macrophages (cells that guide the myelin attack), resulting in reduced relapse rates and improved disability scores (Goldenberg, 2012).

Natalizumab is a monoclonal antibody that reduces the relapse rate in RRMS, slows disease progression, and decreases the number of lesions, but is used only if the disease is very active or if the individual is not responsive to β-interferons or Glatiramer acetate (Rejdak, Jackson, & Giavonnoni, 2010). Natalizumab works by preventing movement of auto-reactive lymphocytes into the brain by blocking binding to vascular cell adhesion molecules (VCAM) which are upregulated on the endothelium during
inflammation and by accelerating repair of the myelin sheath lesions (Rejdak, Jackson, & Giavonnoni, 2010, Polman et al., 2006).

Fingolimod sphingosine-1-phosphate receptor modulator can be prescribed to help reduce relapse rate in RRMS, but is correlated to an increased risk of infection. Fingolimod prevents lymphocytes from migrating out of the lymph nodes and decreases their number in circulation (Goldberg, 2012). This is the only drug approved for treatment of highly active RRMS (Anthony, Jouria, & Houtman, 2014).

Several other pharmacological alternatives are used specifically in relapsing and aggressive types of MS. Dimethyl Fumarate has only been evaluated in relapsing forms of MS and works through oxidative pathways to decrease autoimmunity (Anthony, Jouria, & Houtman, 2014). Teriflunomide, approved in the treatment of RRMS, is an active metabolite of the anti-rheumatic drug leflunomide. Teriflunomide works by inhibiting cell division of specific immune cells (Saguil, Kane, & Farnell, 2014). In treating exacerbations in rapidly progressive MS that are non-responsive to corticosteroid treatment, plasmapheresis (plasma exchange) is used as a secondary treatment (Goodin et al., 2002).

**Symptomatic Therapy**

In addition to treating MS exacerbations and preventing relapse and progression of the disease, symptoms of MS are also managed through pharmacologic and rehabilitative methods.
Treatment of Fatigue

Fatigue is often assessed through self-reported scales such as the Fatigue Severity Scale or the Modified Fatigue Impact Scale. Fatigue is treated pharmacologically by Amantadine or Modafinil; however, drug treatment has limited effectiveness on fatigue (Rejdak, Jackson, & Giavonnoni, 2010; Asano & Finlayson, 2014). Both Amantadine and Modafinil are prescribed off-label in MS and have inconsistent results (“Provigil,” n.d.; “Amantadine,” n.d.; Rejdak, Jackson, & Giavonnoni, 2010). Amantadine is an antiviral drug prescribed to prevent or treat influenza infections, and is also used as supplementary medication in Parkinson’s disease (“Amantadine,” n.d.). Its mechanism of improving fatigue is unidentified (“Amantadine,” n.d.). Modafinil is traditionally used to promote wakefulness in narcolepsy, and has been found to have mixed results in treating fatigue in MS (“Provigil,” n.d.).

Asano and Finlayson (2014) conducted a meta-analysis on 3 types of fatigue management (exercise, education and medication) in MS individuals in order to compare treatment options. Exercise rehabilitation methods including aerobic, aquatic, inspiratory muscle exercise, vestibular rehabilitation program, progressive resistance training, climbing and yoga were found to more effective in improving fatigue than drug therapy (Amantadine and Modafinil). Educational fatigue management including energy conservation strategies (limiting physical activity), fatigue self-management education (client selected strategies to manage fatigue based on their needs, environment and preferences), cognitive behavior therapy (changing patterns of thinking or behavior that
are problematic), and heat sensitivity control (pre-cooling the body, cool environment) demonstrated stronger and more significant effects on reducing the impact and severity of fatigue than medication (Asano & Finlayson, 2014; Hugos et al, 2010).

Hugos and colleagues (2010) found that group sessions conducted with digital video disc (DVD), discussion and homework significantly decreased fatigue and improved self-efficacy in MS individuals. A recent review (Latimer-Cheung et al., 2013) noted the mixed results of treatments on fatigue. Exercise is often thought to improve fatigue, though aerobic training alone did not consistently produce these results (Latimer-Cheung et al., 2013). The authors concluded that optimal dose or training modality is not determined, and they suggested that resistance training may be most effective in reducing fatigue.

**Treatment of Heat Sensitivity**

Heat sensitivity, or Uhthoff phenomenon is a temporary worsening of symptoms when body temperature increases, and is specific to MS (Bol et al., 2012). According to White and colleagues (2000), 58-93% of MS individuals experience a relationship between environmental temperature and fatigue. However, Bol and colleagues (2012) were unable to identify a correlation between environmental temperature and heat sensitivity. Heat sensitivity in MS individuals correlated to disease duration, and decreasing disease severity, whereas sex, age, depression, and physical and mental fatigue did not impact heat sensitive responses (Bol et al., 2012).
Heat sensitivity is managed by lowering body temperature through the environment or by way of cooling devices (Syndulko, Jafari, Woldanski, Baumhefner, & Tourtellotte, 1996). White and colleagues (2000) found that precooling up to the suprailiac crest with water (16-17 degrees C) immersion allowed for a significantly lower exercise heart rate, lower rate of perceived exertion, significant better walk performance after exercise, lower core temperature through 30 minutes post exercise, decreased fatigue and increased exercise comfort in heat sensitive MS individuals.

**Treatment of Spasticity**

Thirty percent of MS individuals experience a level of spasticity that causes them to alter or eliminate their daily activities (Anthony, Jouria, & Houtman, 2014). Spasticity is often measured through the self-reported Modified Ashworth Scale, which describes the resistance to passive stretch (Bohannon & Smith, 1987). Treatment of spasticity aims to decrease hypertonia and pain, as well as improve motor function, and prevent complications including pressure ulcers and contractures (Anthony, Jouria, & Houtman, 2014). Tonic muscle spasms are those where muscle tone is continuously increased, and these types of spasms often respond to sodium-channel blockers (Rejdak, Jackson & Giavonnoni, 2010). Spasticity can be aggravated by sudden position changes, extreme temperatures, humidity, infections, and tight clothing.

Treatment of spasticity in MS includes combinations of medications, physical and occupational therapy, exercise and stretching, adjusting daily activities (Walker, Hall, & Hurst, 1990). Rare cases that don’t respond to treatment may require surgical measures.
Baclofen, a muscle relaxant that targets nerves in the spinal cord, is often the drug intervention of choice used for spasticity in MS (Anthony, Jouria, & Houtman, 2014; Walker, Hall, & Hurst, 1990). Tizanidine is a medication that quickly calms muscle spasms and relaxes tight muscles (Walker, Hall, & Hurst, 1990). Benzodiazepines can also be helpful, however they can cause sedation (Walker, Hall, & Hurst, 1990).

**Treatment for Gait Problems**

Treatment for gait problems includes physical and occupational therapy, rehabilitation, and medications. Therapies often teach correct walking techniques and gait training (Williamson, 2011). Rehabilitation may teach techniques such as energy conservation, the use of adaptive equipment such as canes and walking devices, and adaptations of the environment (Tyler et al., 2014). Spasticity often interferes with gait and mobility, and is treated with stretching and antispasticity medications such as Baclofen or Tizanidine (“NINDS,” n.d.). The drug Ampyra, has been shown to improve walking speed by 20% in all types of MS, however, these effects are only seen in 35% of the individuals tested (Williamson, 2011; “NINDS,” n.d.).

Additionally, in MS, several contemporary electrical stimulation treatments have been tested in treating gait problems. Paul and colleagues (2008) found that electrical stimulation of lower leg muscles to prevent drop foot promoted improvements in gait. Deep brain stimulation where an electrode is implanted in the ventral intermediate nucleus of the thalamus yielded modest and variable results in decreased tremor and
improved gait (Torres et al., 2010; Hu et al., 2010). Vagus nerve stimulation also reduces
tremor and the electrode is placed in the left afferent vagal fibers; whereas the right vagus
nerve innervates the sinoatrial node and would induce cardiac symptoms (Spuck et al.,
2010). However, the cost, invasiveness and side effects limit wide use of these
techniques. Tyler and colleagues (2014) found reduced gait dysfunction in multiple
sclerosis individuals with cranial nerve neuromodulation by using an electrical impulse
placed on the tongue. The authors postulated that by electrically stimulating the
trigeminal and facial cranial nerves, a flow of action potentials to the brainstem and
cerebellum induced neuroplasticity. Neuroplasticity was thought to occur through
stimulating direct collateral connections, improving brainstem interneuron circuitry, and
inducing changes in neurotransmitters and neuroactive compounds (Tyler et al., 2014).

**Treatment for Dizziness**

Dizziness and vertigo in MS may result from lesions in the medullary tegmentum
(near the vestibular apparatus) and the 8th cranial nerve and are treated acutely by
corticosteroids to reduce inflammation (Pula, Newman-Toker, & Kattah, 2013; Frohman,
et al., 2011; “Dizziness and Vertigo,” n.d.). Few reports exist on treatment options for
dizziness and vertigo in MS, however, in the general population, acute vertigo attacks are
treated through vestibular blocking agents which can be used in MS in the short term (Sa
et al., 2011). In addition, anti-motion sickness medications such as Meclizine and skin
patches delivering Scopolamine are used to treat dizziness and vertigo (“Dizziness and
Vertigo,” n.d.). Anti-nausea drugs including Ondansetron are also used to treat dizziness
and vertigo (“Dizziness and Vertigo,” n.d.). Dizziness can be treated symptomatically through physiotherapy, vestibular rehabilitation therapy, and repositioning maneuvers to replace the otoconial mass onto the macular membrane (Sa et al., 2011; Frohman, et al.).

**Treatment for Pain**

Pain often occurs in the form of neuropathic central pain, Lhermitte’s sign, painful tonic spasm, muscular pain, trigeminal neuralgia, headache, and retrobulbar optic neuritis. Neuropathic central pain is treated through antiepileptic and tricyclic antidepressant drugs (i.e.: amitriptyline) (Brola, Mitosek-Szewczyk, & Opara, 2014). If pain is extreme and unresponsive to traditional treatment, surgical techniques have been used to damage zones of the thalamus or to cut dorsal roots in spinal entry areas (Brola, Mitosek-Szewczyk, & Opara, 2014).

Lhermitte’s sign is associated with lesions in the posterior column of the cervical spinal cord and is treated similar to neuropathic pain, or with intravenously injected lidocaine or oral mexiletine (Brola, Mitosek-Szewczyk, & Opara, 2014). A soft collar can be used to limit neck flexion (“Pain,” n.d.).

Spastic pain often occurs as a result of lesions of the basal ganglia, internal capsule, cerebral peduncle, medulla and spinal cord. Antiepileptic drugs, intravenous infusions of lidocaine or local botulinum toxin injections can be used for treatment. Cannabinoids have also been used to reduce spasm, thereby reducing pain (Brola, Mitosek-Szewczyk, & Opara, 2014).
Muscular pain can be a side effect of the medication Beta Interferon, the most common treatment for MS (Brola, Mitosek-Szewczyk, & Opara, 2014). Treatment for muscular pain includes nonsteroidal anti-inflammatory drugs, physiotherapy to stabilize proximal muscles and teach posture, electrotherapy, cryotherapy, magnotherapy, and hydrotherapy (Brola, Mitosek-Szewczyk, & Opara, 2014; “Pain,” n.d.).

Trigeminal neuralgia is a stabbing pain in the face results from demyelinating plaques in the pons and cranial nerve V. Antiepileptic drugs such as carbamazepine are commonly used as treatment (Brola, Mitosek-Szewczyk, & Opara, 2014; “Pain,” n.d.). Surgically radio frequency thermocoagulation, microvascular decompression and gamma knife radio surgery techniques can be used to treat trigeminal and glossopharyngeal neuralgia (Warren, Kotsenas, & Czervionke, 2006). Headache is treated with standard migraine and tension headache medications as in the general population. Retrobulbar optic neuritis results in pain behind the eye due to lesions in the optic nerve. Corticosteroids are used to reduce inflammation in optic neuritis (Brola, Mitosek-Szewczyk, & Opara, 2014).

**Treatment of Visual Problems**

Vision problems including optic neuritis, nystagmus, and diplopia can significantly impact activities of daily living. Optic neuritis is treated by using corticosteroids because of their immunosuppressive and immunomodulatory effects (Brola, Mitosek-Szewczyk, & Opara, 2014; Frohman, 2008). Intravenous methylprednisolone is prescribed followed by a tapered dose of oral steroids such as
prednisone (“Pain,” n.d.). Nystagmus is treated by Baclofen and the use of special prisms (Frohman, 2008; Sa et al., 2011; “Pain,” n.d.). Diplopia typically resolves without treatment, however resting the eyes or use of an eye patch for short durations is helpful (“Pain,” n.d.; Sa et al., 2011).

**Treatment of Cognitive Deficits**

Cognitive deficits can interfere with daily functioning, and are associated with depression, low self-esteem, and impaired social functioning (Kavcic & Scheid, 2011). Cognitive impairment often manifests as poor attention, executive functioning, slowed information processing and reduced memory retrieval (Amann et al., 2011). Kavcic and colleagues (2011) suggested that cognitive deficits in MS are likely due to a reduction of information processing rather than a reduction in working memory. Treatment includes cognitive behavior therapy, psychotherapy and counseling. Amphetamines may improve cognitive performance, and acetylcholinesterases can improve memory impairment (Frohman, et al., 2011). However, a recent meta-analysis by Briken and colleagues (2014) suggested that pharmacological approaches for cognitive impairment in MS were ineffective. Therefore, additional therapeutic options for treatment of cognitive deficits are needed.

Several randomized control trials in healthy young and aging adults have documented improvements in cognitive function after aerobic exercise interventions (Smith et al., 2010). Exercise has been shown to promote neuronal protection and alter MS pathology in the animal model of MS (Rossi et al., 2009). Briken and colleagues,
(2014) compared arm ergometry, rowing and cycle ergometry in moderately disabled Progressive Multiple Sclerosis patients for 8-10 weeks with a frequency of 2-3 times per week. Exercise was found to be feasible with low dropout rates that were not different between the three exercise group and the waitlisted control group (Briken et al., 2014). Improvements in cognitive tonic alertness and VO₂ were only seen in the cycle group, while cognitive improvements in shift of attention, increased walk speed and decreased depression occurred in the arm ergometer and cycle groups (Briken et al., 2014). In addition, cognitive improvements in verbal learning and delayed memory were found in all exercise groups (Briken et al., 2014). Higher fitness levels in Multiple Sclerosis patients are associated with higher structural connectivity and higher gray matter density (Briken et al., 2014). Moreover, fitness may be related to less severe central nervous system damage and higher structural integrity of brain networks that are important to cognitive function (Briken et al., 2014).

**Treatment for Depression**

Depression is commonly assessed through the self-reported Beck Depression Inventory in MS and is treated using a sedating tricyclic antidepressant such as amitriptyline or serotonin reuptake inhibitors (Anthony, Jouria, & Houtman, 2014; Feinstein, 2011; Rejdak, Jackson, & Giavonnoni, 2010). Cognitive behavior therapy develops skills to cope with emotions, thoughts, and adjustments to MS diagnosis and symptoms, and has been found to improve depression (Mohr, Boudewyn, Goodkin, Bostrom, Epstein, 2001; Feinstein, 2011). By incorporating behavioral activation and
cognitive restructuring, cognitive behavior therapy develops fatigue management, management of mild cognitive impairment, pain management, stress management and skills for intimacy in the MS individual (Mohr, Boudewyn, Goodkin, Bostrom, Epstein, 2001). Mindful based intervention encourages a nonjudgmental awareness of everyday moments used to positively impact perception, increase sense of control, and acceptance of health related problems (Feinstein, 2011).

**Treatment of Bowel and Bladder Dysfunction**

Bladder dysfunction is treated through lifestyle modification, physical therapy, medications, and nerve stimulation. Adequate fluid intake should be encouraged, however strategically planning voiding and limiting fluids 2-3 hours before bedtime can be helpful (“Bladder Problems,” n.d.). Bladder training and physical therapy including strengthening the pelvic floor, biofeedback, neuromuscular stimulation, and daily home exercise can be used to reduce urinary urgency, frequency and loss of bladder control (“Bladder Problems,” n.d.). Medications including anti-muscarinics and anticholinergics help with bladder dysfunction, and the tricyclic antidepressant imipramine are used to treat incontinence (Frohman, et al., 2011). Nocturia, having an overactive bladder at night, is treated with oral desmopressin (Frohman, et al., 2011). Percutaneous tibial nerve stimulation requires a small needle electrode inserted in the ankle to stimulate the sacral plexus, and is known to decrease urinary frequency, urgency, nocturia and incontinence (“Bladder Problems,” n.d.). Intermittent self-catherization several times a day by inserting a tube into the urethra to fully empty the bladder is used in cases where
the individual cannot independently empty the bladder completely ("Bladder Problems," n.d.). Suprapubic bladder neck vibration, chemical denervation of the detrusor muscle using either intravesicular capsaicin or botulinum toxin, and intermittent vasopressin are also used to treat bladder dysfunction (Rejdak, Jackson, & Giavonnoni, 2010).

Bowel dysfunction includes constipation or fecal incontinence. Constipation is treated through adequate fluid intake, fiber supplemented in the diet, stool softeners, establishing a schedule, suppositories, and enemas ("Bowel Problems," n.d.; Rejdak, Jackson, & Giavonnoni, 2010). Fecal incontinence is treated through the medication loperamide, biofeedback for pelvic floor muscles and rectal sensory perception, and in cases unresponsive to traditional treatment, surgical colostomy is employed (Frohman, et al., 2011).

**Alternative Therapies for MS**

In addition to traditional pharmacological treatment and rehabilitative treatment, 60% of MS individuals seek alternative treatments (Anthony, Jouria, & Houtman, 2014). One complementary therapy is Vitamin D supplementation. Low vitamin D serum levels have been associated with a higher risk of developing Multiple Sclerosis (Duan et al., 2014). There is also a higher correlation of low vitamin D levels with clinical and brain MRI activity in RRMS (Bhargava et al., 2014). Further research indicates that 50 nmol/L increases in average serum vitamin D levels translated to a 57% decrease in the rate of new active MS-defining lesions (Hanwell & Banwell, 2011). The impact of vitamin D deficiency in MS is thought to be linked to geographical location; those farther from the...
equator and the sun have a higher incidence of MS (Bhargava et al., 2014; Duan et al., 2014; Hanwell & Banwell, 2011).

Deficiencies in vitamin D may impact the instance and onset of Multiple Sclerosis due to its immune and anti-inflammatory roles. Vitamin D is an important immunomodulator that promotes dendritic cells, prevents proliferation and enhances apoptosis of activated B cells, inhibits pro-inflammatory T
\textsubscript{H}1 cells, modulates inflammation, and promotes production of T
\textsubscript{reg} cells (Bhargava et al., 2014). In addition, vitamin D is known to reduce antigen presenting B cells, monocytes and dendritic cells (Bhargava et al., 2014). Though the optimal dose and timing of supplementation to prevent or diminish disease impact remains unclear, vitamin D supplementation does have evidence to support its benefit as an alternative therapy for MS (Hanwell & Banwell, 2011).

Polyunsaturated fat consumption is associated with lower MS prevalence, and omega fatty acid intake may improve MS symptoms (Frohman et al., 2013). However further research is required to substantiate these claims (Frohman et al., 2013). Cannabis can be used to decrease spasticity and MS related symptoms, however this often illegal alternative therapy is controversial due the cognitive side effects (Chong et al., 2006). The herb Ruta graveolens (common rue) has been traditionally used in MS treatment; however, there is no scientific evidence to support its use (Bodendiek, Mahieux, Hansel, & Wulff, 2008). Bee venom provides anti-inflammatory properties, possibly by blocking IL-6 an inflammatory cytokine, but the prohibitive risk of anaphylactic shock outweighs
the small anti-inflammatory benefit (Namaka et al., 2008). Although MS individuals often suffered from poor oxygenation which affected the nerves and impulse conduction, there is no evidence to support improvement with hyperbaric oxygen therapy (Bennett & Heard, 2004).

Multiple Sclerosis focal lesions develop from an autoimmune response driven by lymphocytes that permeate the blood brain barrier, and attack the myelin sheath. Antioxidants can reduce the permeability of the blood brain barrier, and MS individuals are often found to have reduced levels of antioxidants (Offen, Gilgun-Sherki, & Melamed, 2004). It seems plausible that supplementation of antioxidants, specifically uric acid which protects the blood brain barrier would be a viable alternative therapy, but further research is needed (Offen, Gilgun-Sherki, & Melamed, 2004; Koch & De Keyser, 2006). Lintas and colleagues (2013) used ozone therapy to trigger mild oxidative stress which induces the production of antioxidants and antioxidant enzymes to protect the cells and reverse chronic oxidative stress. They concluded that ozone promotes the reduction of oxidative stress and enhanced mitochondrial functionality in MS individuals.

A final supplementary alternative therapy is acupuncture which reduces pain and muscle spasm resulting in improved quality of life (Quispe-Cabanillas et al., 2012). However, additional research is needed to determine appropriate usage of acupuncture in MS.
Exercise and MS

Despite proven benefit of exercise on the symptoms of MS, there are several barriers to physical activity in this population. Multiple Sclerosis individuals have a lower aerobic capacity, lower muscle strength, slowed rate of muscle tension development, lower muscle endurance and impaired balance when compared to healthy individuals (Doring, Pfueller, Paul, Dorr, 2012). Indicative of compromised fitness levels, Kuspinar and colleagues (2010) found VO2 max in Multiple Sclerosis individuals is below the 25th percentile. A further concern is that 40% of MS individuals require some form of walking assistance within 15 years of disease onset (Tyler et al., 2014).

Pharmacologically, Interferon B and Glatiramer Acetate are only partially effective in treating MS symptoms, necessitating additional treatment options (Rudick et al., 2006). Traditionally, exercise has been avoided in the MS population because of acute transient problems with mobility, weakness, and fatigue after exercise (Hayes, Gappmaier, & LaStayo, 2011). Although previous recommendations suggested that exercise exacerbated symptoms, current research challenges this view and demonstrates that exercise is beneficial (Pilutti et al., 2011). In fact, limits on physical activity in this population can lead to greater weakness, fatigue, and health risks that result from deconditioning (Mostert & Kesselring, 2002).

Physical activity decreases morbidity and mortality in healthy populations, and likely has similar effects on people with Multiple Sclerosis (Bjarnadottir, Konradsdottir, Reynisdottir, & Olafsson, 2007). Exercise has the capacity to slow disease progression
and improve various aspects in the physiological profile of Multiple Sclerosis, and is well tolerated with low occurrence of adverse effects (Kargarfard, Etemadifar, Baker, Mehrabi, & Hayatbakhsh, 2012; Doring, Pfueller, Paul, Dorr, 2012).

Prakash and colleagues (2010) discovered a positive correlation between higher fitness and gray matter volume, higher scores on composite measures of information processing speed, and an inverse relationship with brain tissue damage in MS. The authors concluded that fitness exerts a prophylactic influence on cerebral atrophy that occurs early in the disease process, thereby, preserving neuronal integrity in MS and reducing long-term disability.

Individuals with Multiple Sclerosis have a normal cardiovascular response to exercise and have the ability to improve fitness (Mostert & Kesselring, 2002). Bjarnadottir and colleagues (2007) demonstrated that a brief 5 week aerobic and strength training program improved physical fitness in mild MS. However, it has been observed that MS individuals have a low anaerobic threshold, low maximal volume of oxygen, and high energy consumption, as well as a high heart rate reserve compared to healthy controls (Mostert & Kesselring, 2002). Although MS individuals have an inability to stress the cardiovascular system maximally, it has been shown that exercise lowers oxygen consumption, heart rate, and increases oxygen pulses (VO2/HR) at a given work rate, indicating an improved aerobic system (Mostert & Kesselring, 2002).

Pilutti and colleagues (2011) found that 12 weeks of body weight supported treadmill training in extremely disabled MS individuals exhibited gait and mobility improvements
Physical activity may help improve physical function and ease psychosocial burdens for those with the disease, as well as for their caregivers and companions (White, Castellano, McCoy, Patel, & Giacobbi, 2012).

Exercise improves and maintains muscle strength, balance and mobility in elderly individuals including those with neurological disabilities (Hayes, Gappmaier, & LaStayo, 2011). A variety of exercise modalities and programs, including yoga, are known to improve quality of life and reduce fatigue in MS individuals (Asano & Finlayson, 2014). After review of 600 participants in diverse exercise modalities and protocols, Snook and Motl (2009) concluded that exercise training programs are associated with small clinically meaningful improvements in mobility of walking in MS individuals.

Currently there are no specific recommendations for exercise treatment that are universally valid; only general therapeutic recommendations exist (Doring, Pfueller, Paul, Dorr, 2012). The primary goal of rehabilitation in MS is to increase activity levels and participation while promoting independence (Reitberg, Brooks, Uitdehagg, & Kwakkel, 2011). However there are several barriers to exercise in the MS population, including change in medication, holidays, surgery, lack of motivation, lack of support system and social support (White, Castellano, McCoy, Patel, & Giacobbi, 2012).

Although exercise is associated with increased fitness, decreased motor fatigue, improved quality of life and psychological conditions (Kargarfard, Etemadifar, Baker, Mehrabi, & Hayatbakhsh, 2012), it is also found to lower cardiovascular risk factors such
as heart disease and obesity. Reitberg and colleagues (2011) reviewed nine high quality randomized control trials and found good evidence for improved muscle power, aerobic fitness, physiological cost index, rate of perceived exertion and mobility related activities. Moderate evidence to support improved mood, anxiety and depression was also present. However, this review yielded little evidence to support that exercise improved fatigue, perception of the handicap, or that specific programs are more successful in improving MS activities and participation; contradicting studies showing improvements in fatigue (Reitberg, Brooks, Uitdehagg, & Kwakkel, 2011). Nevertheless, no evidence for negative effects of exercise was found.

**Mechanisms of Exercise Induced Improvements in MS**

Exercise believed to produce improvements in MS by enhancing the immune system functioning, increasing growth factors (BDNF, IGF, VEGF, and NGF) and improving motor learning. During moderate exercise there is a rise in peripheral lymphocytes which then decrease below the initial levels after the exercise is complete (Doring, Pfueller, Paul, Dorr, 2012). The decrease in lymphocytes after exercise is short (3-24 hours) which emphasizes the need for a consistent exercise program in MS individuals. The lymphocytes that decrease after exercise are T-helper (Th) cells which aid the immune system in distinguishing foreign from self and aiding the interactions between cells fighting foreign materials. There are many different types of T-helper cells, and two of interest in MS are Th1 cells and Th2 cells. Th1 cells exhibit a pro-inflammatory effect and Th2 cells produce an anti-inflammatory response (Doring,
Pfueller, Paul, Dorr, 2012). Exercise is especially beneficial in MS because there are declines in Th1 cells rather than Th2 cells (Doring, Pfueller, Paul, Dorr, 2012). This is relevant to the MS pathogenesis due to the inflammatory autoimmune attacks on the myelin sheath. Immuno-modulatory drugs exert a similar response and may be complemented by exercise (Doring, Pfueller, Paul, Dorr, 2012). Regular and frequent training intervals may be beneficial due to the transitory effects of exercise (Doring, Pfueller, Paul, Dorr, 2012).

Exercise also stimulates the production of brain derived neurotropic factor (BDNF), Insulin-like growth factor (IGF), and vascular endothelial growth factor (VEGF). These growth factors enhance cell proliferation, synaptic plasticity, neuroprotection, and neurogenesis in physiological and neuro-inflammatory conditions (Doring, Pfueller, Paul, Dorr, 2012). During human development, IGF-1 supports cell survival, brain growth, and central nervous system myelination (Doring, Pfueller, Paul, Dorr, 2012). Later in the adult, IGF-1 may be neuroprotective and aid synaptic and cognitive neuroplasticity (Doring, Pfueller, Paul, Dorr, 2012). Doring and colleagues (2012) documented increased BDNF and nerve growth factor (NGF) after thirty minutes of moderate ergometry based exercise in healthy and MS individuals. IGF-1 increased after exercise in healthy individuals, but has not been tested in MS individuals (Doring, Pfueller, Paul, Dorr, 2012).

Doring and colleagues (2012) also found increased levels of BDNF in the hippocampus, possibly aiding learning, memory, modulation of mood, and may have the
capability to slow cognitive decline. There is evidence of a reduction in serum BDNF during MS relapses compared to periods of remission (Prakash, Snook, Motl, & Kramer, 2010). In fact depression in MS individuals is possibly linked to reductions in BDNF (Prakash, Snook, Motl, & Kramer, 2010). In addition, exercise may help to attenuate reductions in BDNF and additional neuroplasticity factors while having a positive effect on modulating stress which is associated with increased relapse risk in MS.

In addition to the growth factors mentioned above, there are other benefits to exercise in the MS population. Exercise has also been found to increase antioxidant enzymes which have a neuroprotective effect (Doring, Pfueller, Paul, Dorr, 2012). Through the repetitive movement of exercise, cortical neural pathways are strengthened, neuroplastic adaptive processes occur and there is improved motor unit activation and synchronized firing rates (Doring, Pfueller, Paul, Dorr, 2012). During times of inactivity these improvements have been shown to decline (Doring, Pfueller, Paul, Dorr, 2012).

The mechanism of exercise induced improvements in MS may result from task specific movements, improved fitness, or improved motor control. Motor learning is skill specific, as skill acquisition theory hypothesizes that in order to achieve mastery of a movement, one must practice the specific task (Lord, Wade, & Halligan, 1998). Lord and colleagues (1998) compared the effects of task specific therapy and facilitation therapy on mobility and balance in MS. The facilitation group received proprioceptive feedback from a therapist to correct deficiencies in posture, balance, and muscle contraction (Lord, Wade, & Halligan, 1998). The task specific group practiced a specific
skill (walking) to achieve mastery (Lord, Wade, & Halligan, 1998). Both the task specific group and facilitation group showed improvements in mobility and balance in MS.

Van den Berg and colleagues (2006) utilized a four week treadmill aerobic intervention that was found to improve gait speed significantly. It is unclear whether task specificity, improvements in fitness, or enhanced motor control were responsible for the improved gait speed, or the resulting trend toward increased endurance and toward decreased fatigue. This study demonstrated that treadmill exercise which is task oriented specific to walking, showed improvements in these parameters during the exercise training, though it was inconclusive in determining the mechanism for the improvements. Furthermore, four weeks post exercise, walking performance returned towards baseline indicating a need of continued exercise (van den Berg et al., 2006).

In relapsing-remitting forms of MS, partial spontaneous repair of demyelination can occur. It is theorized that repair is a result of neuroplasticity in which axons and dendrites undergo collateral sprouting (Herbert, Corboy, Manago, & Schenkman, 2011). This appears to be enhanced through task specific rehabilitative training (Herbert, Corboy, Manago, & Schenkman, 2011). An additional benefit of exercise is improved motor control which may lessen the effects of motor fatigue on anticipatory postural adjustments (Herbert, Corboy, Manago, & Schenkman, 2011).

Gait and mobility are further impacted by dizziness and deficits in postural control that are controlled by central sensory processing (Herbert, Corboy, Manago, &
Impaired upright postural control is linked to poor central sensory integration and fatigue in MS (Herbert, Corboy, Manago, & Schenkman, 2011). Rampello and colleagues (2007) utilized an 8 week training protocol with mild to moderate disability MS individuals to compare progressive aerobic training to a neurological (postural) rehabilitation group undergoing respiratory-postural, respiratory-motor synergies training, and stretching. The authors found that lung function and respiratory muscle strength did not change in either group, but the aerobic training group experienced increases in walking distance, speed, and aerobic fitness parameters, whereas the neurological rehabilitation training group did not (Rampello et al., 2007). Fatigue and health related quality of life were also unchanged in either group (Rampello et al., 2007).

Lesions in the brainstem and cerebellum lead to visual somatosensory and vestibular processing impairments (Herbert, Corboy, Manago, & Schenkman, 2011). Of MS individuals, 85% experience peripheral deficit vestibulopathy (Herbert, Corboy, Manago, & Schenkman, 2011). Primary fatigue, caused directly by the disease process may be better treated by vestibular rehabilitation depending on location of the lesions. Herbert and colleagues (2011) used a 6 week intervention to compare three groups. The first group underwent vestibular rehabilitation and saw improvements in fatigue, impaired balance, and disability due to dizziness and disequilibrium. The second group exercised using a cycle ergometer and underwent stretching. This group, along with the vestibular rehabilitation group experienced improvements in depression. The third group served as a control and continued with usual medical care. All three groups improved in
mobility which may have resulted from factors outside of the study (such as walking to the testing site) (Herbert, Corboy, Manago, & Schenkman, 2011).

Regular exercise may also have an important role in managing fatigue, mental alertness, and cognitive processing (Paul et al, 2014). Results on walking endurance and speed due to exercise are promising though the benefits on agility are less clear (Latimer-Cheung et al., 2013). It is likely that the mixed results found in current studies are due to the varying length of training periods and the degree of disability of MS individuals in the studies (Rampello et al., 2007).

**Aerobic Training in MS**

Aerobic training produces an increase in peak oxygen uptake, increase in muscle strength and endurance, decrease in fatigue, increase in activity level and improvements in balance and gait patterns in individuals with MS (Hayes, Gappmaier, & LaStayo, 2011). Cakit and colleagues (2010) found aerobic training effective in improving mobility, functional reach, walking endurance while decreasing fatigue and disability levels. Treadmill training resulted in improvements in strength, spasticity, walk speed and endurance, balance and quality of life in MS individuals (Cakit et al., 2010). Carter and White (2003) demonstrated that a 12 week general aerobics program reduced physiological cost index and increased muscle strength in specific muscle groups. O’Connell and colleagues (2003) determined that a similar 12 week aerobic protocol improved muscular fitness and quality of life, pre and post heart rate, gait cadence, and RPE without a change in gait speed in the exercise group compared to controls.
Aerobic activities also have a positive impact on cardiovascular risk factors, obesity, all-cause mortality, osteoporosis, depression and diabetes mellitus (Mostert & Kesselring, 2002). Depression and anger scores of the Profile of Mood States were significantly decreased after 15 weeks of aerobic training in a study done by Petajan and colleagues (1996). Schulz and colleagues (2004) showed that an 8 week low level bicycle aerobic exercise protocol improved fitness and disease specific quality of life in MS individuals. Latimer-Cheung and colleagues (2013) completed an extensive review of the exercise literature and recommended 2-3 sessions per week for 30 to 60 minutes in duration of moderate intensity defined as 60-80% max work rate or VO2 maximum to improve aerobic fitness in MS. This is consistent with ACSM guidelines for the general population to improve fitness including 20-60 minutes 3-5 times per week at 40-50% maximal VO2.

Aerobic training is also associated with changes in brain structure. MS individuals with high aerobic fitness showed larger gray matter volumes of the right post-central gyrus and midline cortical structures than unfit MS individuals. The higher fitness was correlated with greater recruitment in cortical regions whereas lower fitness was associated with greater anterior cingulated cortex recruitment (Solari et al., 1999). In addition, MS individuals exhibit more brain areas bilaterally activated compared to non-multiple sclerosis individuals, indicating that MS individuals adapt through neuroplasticity. The bilateral activation is correlated to MS disease and severity (Doring,
Aerobic exercise may play a profound role in assisting and enhancing neuroplasticity in MS individuals (Doring, Pfueller, Paul, Dorr, 2012).

**Resistance Training in MS**

Resistance training generates increased muscle strength and power while reducing the perception of fatigue (Hayes, Gappmaier, & LaStayo, 2011). In other special populations (Parkinson Disease, Cancer, Stroke) improvements in strength resulted in improvements in mobility, balance and function. However, resistance training in MS individuals has uncovered mixed results for balance, gait pattern, and functional capacity (Hayes, Gappmaier, & LaStayo, 2011). Jones and colleagues (1999) compared a weighted leg exercise treatment, mobility exercise program, and a control group and found there were no significant differences in gait, ability to transfer and muscle strength. DeBolt and McCubbin (2004) used an 8 week home based resistance exercise program to increase leg extensor power in MS, and concluded there were no significant differences in mobility and balance compared to control subjects. It is possible that motivation and adherence played a significant role as home based studies are not as effective as outpatient or inpatient rehabilitation sessions. Individuals in an unsupervised environment are less likely to change their training program in order to develop adequate workload progression, which is essential for adaptation (Latimer-Cheung et al., 2013).

In contrast to the above studies, Solari and colleagues (1999) compared 3 weeks of inpatient exercise therapy followed by home rehabilitation to a group practicing exclusively home exercise, and found the inpatient group had significant improvements
in disability, motor domains and mental components of quality of life. White and colleagues (2012) used a 4 month resistance training protocol in MS women that improved walking measures, and qualitatively found that exercise may be effective in attenuating loss or improving daily function. They reported MS individuals were motivated to exercise by a desire to maintain function and health, enhanced exercise self-efficacy, feelings of hope and optimism, and the presence of role models.

MS responds to eccentric resistance exercises differently than other populations. Eccentric exercise is when the muscle lengthens during the contraction. Hayes and colleagues (2011) developed RENEW, an eccentric resistance training program but found that eccentric exercises were not beneficial in individuals with MS, despite the fact that it was beneficial in people with Parkinson’s disease. The authors theorized that the MS deficiency in improvements in functional activities were due to the central nervous system’s lost capacity to respond to higher intensity forces.

Overall, strength training promotes neural adaptation, better motor unit activation, and synchronization of firing rates (Hayes, Gappmaier, & LaStayo, 2011). Latimer – Cheung and colleagues (2013) concluded in their review that resistance training eliciting muscular strength improvements should be 8-20 weeks long, 2-3 times per week, with 10-12 repetition maximum.

Cakit and colleagues (2010) examined the benefits of progressive resistance using the cycle ergometer in MS individuals (16). Improvements in duration, maximal workload, Timed up and Go test (TUG), Dynamic Gait Index (DGI), functional reach,
falls efficacy (a self-reported scale), 10 minute walk test, Fatigue Severity Scale, and Beck Depression Inventory were documented. The authors concluded that pharmacology alone is not optimal and that exercise is a feasible form of self-management for persons with Multiple Sclerosis (Cakit et al., 2010).

Although traditional land-based aerobic and resistance training programs have been shown to benefit individuals with MS, the risk of overheating, extreme fatigue and falling makes regular exercise a challenge for these individuals. MS individuals are limited by high impact exercise due to unpredictable relapse and pain. The aquatic exercise environment increases body heat dissipation, provides buoyancy, decreases joint stress, and decreases fear of falling. Aquatic exercise has been found feasible and beneficial in the MS population (Kargarfard, Etemadifar, Baker, Mehrabi, & Hayatbakhsh, 2012).

**Aquatic Exercise and MS**

Aquatic exercise is recommended by the American Physical Therapy Association in treatment of Multiple Sclerosis (Kargarfard, Etemadifar, Baker, Mehrabi, & Hayatbakhsh, 2012). The buoyancy and viscosity of water assist the activities of those who have physical weakness (Kargarfard, Etemadifar, Baker, Mehrabi, & Hayatbakhsh, 2012). In addition, the increased ability to dissipate body heat in the water aids in diminishing Uhthoff phenomenon (Kargarfard, Etemadifar, Baker, Mehrabi, & Hayatbakhsh, 2012). Aquatic therapy reduces joint stress and decreases the fear of falling (Plecash & Leavitt, 2014). Aquatic exercise reduces the effects of gravity,
allowing individuals with severe paresis to perform standing and moving exercises (Doring, Pfueller, Paul, Dorr, 2012). Aquatic therapy generally includes stretching and range of motion, aerobic, resistance and strength training in a shallow pool (Plecash & Leavitt, 2014). Despite these positive characteristics of exercising in water, only 1.5% of MS individuals use water therapy (Plecash & Leavitt, 2014).

Aquatic exercise with varying frequency, duration, intensity and mode have been investigated in the MS population. Kargarfard and colleagues (2012) found that in RRMS patients, 8 weeks of aquatic aerobic activity was feasible, improved fatigue, and improved health related quality of life parameters. Fatigue and health related quality of life measures were taken at baseline, at 4 weeks and at 8 weeks. While there was a trend toward improvement in these parameters at 4 weeks, significant differences were observed at 8 weeks of aquatic exercise (Kargarfard, Etemadifar, Baker, Mehrabi, & Hayatbakhsh, 2012). Aquatic exercise lasting for six weeks was found to have a positive impact of sickness (Mostert & Kesselring, 2002). Romberg and colleagues (2004) used a 6 month aerobic training protocol including aquatic exercise and strength training, which resulted in increased walk speeds compared to individuals not undergoing therapy. Roehrs and Karst (2004) used a 12 week aquatic warm water (85 degrees F) intervention and demonstrated a significant improvement in quality of life specifically in fatigue and social functioning. Sixty minutes of aquatic class time, twice a week was used with progressive MS individuals (Roehrs & Karst, 2004). Marinho-Buzelli and colleagues
(2014) used aquatic therapy in 20 MS individuals, and demonstrated a fair ability to improve gait speed.

Non-traditional aquatic exercise has also been investigated in MS. Castro-Sanchez and colleagues (2012) used Ai Chi aqua therapy in MS two times per week for twenty weeks. Ai-Chi aquatic exercise was used two times per week for twenty weeks. Ai Chi is deep breathing combined with slow broad movements to work on balance, strength, relaxation, flexibility and breathing. They compared the Ai-Chi exercise group to a control group that performed abdominal breathing and contraction and relaxation exercises in the therapy lab, and found improvements in pain, spasm, fatigue, disability and autonomy in the Ai-Chi group (Castro-Sanchez et al, 2012). Bansi and colleagues (2012) compared land cycling to aquatic cycling and found increased serum levels of BDNF in the aquatic group, but not in the land based group. Subjects in this study worked at 70% maximum heart rate for 30 minutes, five times per week for 3 weeks. Salem and colleagues (2011) used a 5 week, 2 times per week for 60 minutes protocol that used aquatic aerobic, strength, flexibility and balance, and walking and showed improved gait speed, Berg Balance Scores, timed up and go, and grip test.

Research literature reveals benefits of aquatic therapy, however there are no specific recommendations for MS treatment (Doring, Pfueller, Paul, Dorr, 2012). With current research studies employing 3 or more weeks of exercise, there is a need to determine the minimal duration required to manifest exercise benefits. Seven
consecutive days of exercise may be beneficial in improving fitness, mobility, and self-efficacy.

**Summary**

Multiple Sclerosis is an autoimmune, demyelinating disease that can impact activities of daily living. Symptoms include fatigue, heat sensitivity, muscle spasms, decreased physical activity, gait problems, dizziness or vertigo, vision problems, pain, cognitive impairments, depression and bowel and bladder dysfunction. Although there is no cure for MS, treatments aim to slow disease progression and lessening the symptoms. Treatments include pharmacological, alternative therapies, and exercise. Exercise can improve fitness, preserve motor and cognitive function, and enhance quality of life. Aquatic exercise has been recommended by the American Physical Therapy Association in the treatment of MS, however, currently only general exercise recommendations exist for MS patients. MS individuals may benefit from moderate to high intensity short duration exercise between relapses. Research has demonstrated exercise induced improvements on gait parameters and quality of life within a 4 week protocol, however, no studies to date have used a one week protocol (Berg 23, Mostert 22). Previous work done by Fedor (2014) produced positive results in fitness and cognitive parameters in a similar aquatic aerobic one week exercise protocol in older adults. However this has not been explored in the MS population. Currently there is no research determining the benefits of short duration aquatic exercise on mobility, cardiovascular fitness, cerebral
oxygenation, or self-efficacy. Benefits resulting from this protocol have the potential to impact the MS population and the use of exercise as treatment.
CHAPTER III

METHODOLOGY

Recruitment

Participants were recruited for the study by placing fliers in the waiting rooms at Neurology and Neuroscience Associates (NNA) facilities and the OAK Clinic. In addition, researchers met with local MS support groups and distributed fliers to prospective participants. Fliers were placed strategically around town in area businesses and churches, and a study overview was placed in the MS Connector. Twitter and Facebook accounts were also set up with the MS study information. The study fliers included research contact information and a physician approval form. Interested MS patients were instructed to contact the research staff after obtaining physician consent to participate in the study (Figure 1). A researcher conducted a telephone prescreening interview in which interest was assessed in addition to discussing inclusion and exclusion criteria and general information on the research study. At the conclusion of the phone interview, the researcher scheduled the prospective participant for their first visit at the Kent State Exercise Physiology Lab to sign the informed consent and the HIPAA release, and for baseline testing.
Recruitment: fliers placed in Dr. Office, MS support groups

Patient responds through email or phone to express interest

Patient is called to: confirm interest in study, inclusion and exclusion criteria

Physician approval required

randomized to exercise group (n = 12)

randomized to control group (n = 9)

Patient not interested; does not meet inclusion criteria; or has exclusion criteria

Patients without physician approval or do not meet inclusion or exclusion criteria: EXCLUDED

Figure 1. Procedures to Recruit Subjects
Inclusion

Only individuals who were diagnosed with Multiple Sclerosis by a physician were included in the study. Participants were required to obtain approval from their physician prior to participating in the study. In addition, participants were between the ages of 20 to 65. To aid the communication within the study, subjects were required to be English speaking.

Exclusion

Exclusion criteria included: females who were pregnant or at risk for becoming pregnant, psychiatric illness, 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.

Risk Minimization

Current research indicated that exercise is feasible in the MS population, and has demonstrable fitness benefits (Pilutti et al., 2011). Aquatic therapy is recommended by the American Physical Therapy Association for therapy in MS patients. The buoyant effect of the water is helpful in reducing gravity and resistance against body movements resulting in longer endurance with less fatigue (Kargarfard, Etemadifar, Baker, Mehrabi, & Hayatbakhsh, 2012). In addition, this study followed a similar protocol to the aquatic MS study done by Kargarfard and colleagues (2012), who concluded that this aquatic protocol was feasible in the MS population.
There was an extremely small risk in exercise of serious medical complications, including heart attack and sudden death. However, the requirement of physician’s approval and participation in a well-organized and individualized exercise program greatly reduced these already small risks. Small risk was present with exercising in the water, however all exercise took place in the shallow end of the pool, and trained staff and researchers (lifeguards, special population trained aquatic aerobics instructor, and trained AED/CPR certified research staff) were present during exercise. Participants were instructed to inform a research team member if they wished to stop, experienced concern regarding exercise equipment or facilities, or happened to experience any of the following during the study: chest pain, shortness of breath, pallor, fainting, wheezing, leg cramps, light-headedness, confusion, nausea, cold/clammy skin, noticeable change in heart rhythm, severe fatigue, or any other discomfort.

A certified special population aquatic aerobics instructor led the small group of 6-10 subjects. Subjects were monitored by a lifeguard in addition to at least two trained research staff. The subject to researcher ratio (2:1) was low to ensure adequate attention and monitoring of each subject. Close supervision and encouragement was essential for MS patients during exercise due to concerns that exercise may have exacerbated their symptoms (Paul et al, 2014). Subjects were instructed about target training intensities and encouraged to self-monitor in order to stay within the range of 65-75% age adjusted maximal heart rate (AAMHR). In addition, the research staff monitored the MS subject’s heart rate and rate of perceived exertion (RPE) every 9 minutes throughout the exercise
protocol. The exercise protocol was an interval protocol which provided rest periods between four minute segments of exercise allowing for recovery time during the exercise. If the heart rate reached greater than 75% AAMHR during the assessments, the subject was required to rest at the side of the pool while being monitored by the researcher. The subject was allowed to return to exercise when the heart rate was at 65% AAMHR. In addition, if RPE is greater than 17, the subject was required to rest at the side of the pool while being monitored by the researcher. The subject was allowed to return to exercise when the RPE was at 13. For additional security, subjects were allowed to hold onto a pool noodle while performing leg exercises. Relationships were established between the researcher and the subject so that subjects were comfortable communicating concerns about the exercise exertion.

**Protocol**

After patients responded to fliers placed in the physician office and MS support groups, they were called by the researcher to determine interest, to discuss inclusion and exclusion criteria, and to provide information on the study. Subjects were responsible for obtaining physician approval prior to participating in the study, and a physician approval form was provided on the back of the MS flier. Individuals who met the inclusion criteria, did not exhibit any exclusion criteria, and were interested in participating were asked to visit the Kent State Physiology lab to learn more about the study and to sign an informed consent and HIPPA release form, and undergo baseline testing on day 1. Baseline testing included body mass index, waist circumference, waist to hip ratio, 25
foot walk test, 2 minute step test, resting heart rate, heart rate variability, blood pressure, and timed up and go test. In addition, assessments of rate of perceived exertion, cerebral oxygenation, and tympanic temperature were recorded, and the self-reported Multiple Sclerosis Self Efficacy Scale was completed by the subject. Subjects were randomly assigned to the exercise or control group. Subjects randomized to the control group were asked to maintain their current lifestyle including their physical activity levels for days two through 8. On the ninth day they reported back to the lab for post-test measures; repeating the same measures as on day one. The exercise group underwent baseline testing on day 1, and participated in aquatic exercise for days two through eight. On day nine they repeated the measures of baseline testing again.

**Exercise and Physiological Variables**

While the control group maintained their current lifestyle, the exercise group participated in seven days of moderate to high intensity aquatic exercise. Table 3 lists the exercise protocol and assessments. Exercise comprised 10 minutes of warm-up consisting of walking and stretching in the water. The warm up was followed by 40 minutes of exercising at 65-75% age adjusted maximal heart rate. Heart rate was measured using a Polar Heart Rate monitor FT1 in the pool. The workout portion of the exercise consisted of 7 x 4 minute intervals with each interval separated by a one minute rest period similar to interval training done by Carter and colleagues (2014). Intervals 1, 3, 5, and 7 focused on aerobic exercise consisting of structured walking at different speeds with or against the current and even jogging. 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.
**Table 3**

*Exercise Protocol and Assessment*

<table>
<thead>
<tr>
<th>Protocol Interval</th>
<th>Time</th>
<th>Subjects will be performing</th>
<th>Target HR/RPE</th>
<th>Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-exercise</td>
<td></td>
<td>On Pool deck prior to aquatic exercise</td>
<td></td>
<td>Tympanic temperature, RPE, HR</td>
</tr>
<tr>
<td>Warm Up</td>
<td>0-10 min</td>
<td>Walking and stretching in water</td>
<td>30-40% Age Adjusted Max Heart Rate</td>
<td>At end of warm up RPE and HR</td>
</tr>
<tr>
<td>Exercise</td>
<td>Measure at the 2nd, 4th, 6th and 8th rest period (every 9 minutes)</td>
<td>Minutes 10-50-Cardiovascular endurance and strength training and range of motion exercises for upper and lower body intervals. 8 X 4 min intervals with 1 minute rest (similar to interval training in <em>Carter et al.</em>, 2014)</td>
<td>65-75% Age Adjusted Max Heart Rate If heart rate is greater than 75% AAMHR, or RPE greater than 17, the subject must rest at the side of the pool while being monitored by the researcher. The subject may return to exercise when the heart rate is at 65%, or RPE is at 13. The subject will be closely monitored with additional heart rate checks (every 5 minutes) as needed.</td>
<td>RPE and HR at each rest period, every 9 minutes Tympanic Temperature at 5th interval only</td>
</tr>
<tr>
<td>Cool Down</td>
<td>50-60 minutes</td>
<td>Walking and stretching in water</td>
<td>30-40% Age Adjusted Max Heart Rate</td>
<td>RPE and HR</td>
</tr>
<tr>
<td>Post exercise</td>
<td>As they trickle out of pool</td>
<td>On Pool Deck after aquatic exercise</td>
<td>Heart rate must be below 40% age adjusted max heart rate in order to remove the heart rate monitor and go home.</td>
<td>HR, RPE and Tympanic</td>
</tr>
</tbody>
</table>
Body Composition

Subjects were assessed in body composition through body mass index, waist circumference, and waist to hip ratio. Body mass index (BMI) is a measure of body fat based on height and weight that applies to adults. Height was plotted against the individual’s weight to assess where they fall on the BMI scale. Body mass index in adolescence has been correlated to incidence of MS (Munger, Chitnis, & Ascherio, 2009). BMI and waist to hip ratio is recommended by an International Consensus Meeting on the core measures in MS (Paul et al, 2014).

The measurements to determine waist circumference were taken just above the iliac crest at the end of exhalation. Measures were at the waist (midpoint between lower margin of the last palpable rib and the iliac crest with a stretch resistant tape providing 100g tension) and Hip (widest portion of the buttocks with take parallel to the floor). Measures were taken with the individual standing, feet together, arms at sides at the end of expiration. Two measures were recorded and if within 1 cm of each other, the measures were averaged. If the measures are not within 1 cm, the measurements were retaken.

Heart Rate and Training Intensity

A Polar Heart Rate Monitor was used to record resting heart rate and heart rate variability during the first and final visits. Resting heart rate reflects the cardiovascular health of an individual. A lower heart rate correlates to more efficient heart function and better cardiovascular fitness.
Heart Rate Variability (HRV) was recorded using a Polar Heart Rate Monitor RS800CX™. HRV is the rhythmic periodicity of the sinoatrial neural discharge that is regulated by the balance between the sympathetic and parasympathetic autonomic nervous system (Meersman, 1993; Cygankiewicz & Zareba, 2013). HRV decreases with aging by shifting to sympathetic dominance, while aerobic exercise maintains and augments HRV (Meersman, 1993). As the body adapts to aerobic exercise, there is a decrease in resting heart rate and an increase in HRV. Aerobic exercise improves cardiovascular function by increasing the efficiency of the heart and increasing parasympathetic regulation which is beneficial to the MS population. HRV is significantly lower in MS individuals indicating a loss of vagal tone and increase in sympathetic tone (Cygankiewicz & Zareba, 2013). The autonomic dysfunction is associated with plaques in the brainstem and spinal cord and the degree of autonomic impairment increases with advancement of the disease (Cygankiewicz & Zareba, 2013). Mahovic and Lalusic (2007), found a significantly lower HRV in MS individuals with a diagnosis of 5 years or greater as compared to those with a shorter duration of the disease.

Heart rate was used to determine exercise training intensity as calculated through the Karvonen Method: $\left(220 - \text{age}\right) - \text{resting heart rate to determine the heart rate reserve. The target heart rate was determined by: } \left[\text{heart rate reserve} \times \text{training }\%\right] + \text{resting heart rate} \right)$ (Karvonen, Kentala, &Mustala, 2007). Subjects were encouraged to work at 65-75% age adjusted maximum heart rate during the interval workout. Mostert
and colleagues (2002) determined that it was a safe and efficient training intensity to work at anaerobic threshold (as determined by gas exchange) in MS individuals.

For the exercise group, heart rate was monitored before getting into the water, after the warm up, every 9 minutes throughout the exercise session, after the cool down, and again on the pool deck after the entire exercise session was completed. MS participants were instructed on target training intensity, and encouraged to self-monitor heart rate and adjust intensity level as appropriate. Individuals that reach a target heart rate at or greater than 75% AAMHR or an RPE greater than 17 were required to stand along the wall while being monitored by the researcher. They were allowed to return to exercise when their heart rate was 65%, and RPE was at 13. The subjects were closely monitored to ensure they do not exercise to exhaustion. Upon completion of the exercise session, heart rate was required to be below 40% age adjusted max heart rate in order to remove the heart rate monitor and go home.

**Rate of Perceived Exertion**

Rate of Perceived Exertion 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, the subject indicated his/her intensity level by pointing out numerically where he/she was on the scale. Rate of Perceived Exertion was assessed using Borg’s Rate of Perceived Exertion Scale at the same time intervals the HR was measured. Solari and colleagues (1999) recommend that MS patients work at a moderate exertion level of 11-14 on the Borg scale.
Mobility Assessments

The Timed 25 Foot Walk (T25-FW) is the first test in the Multiple Sclerosis Functional Composite (MSFC). The MSFC is used to measure lower limb function (T25-FW), upper limb function (9 hole peg test), and cognitive function (Paced Auditory Serial Addition Test) (Potter et al., 2012, Kieseier & Pozzilli, 2012). The T25-FW is a quantitative mobility and leg function performance test based on a timed 25-walk. The patient was instructed: “I’d like you to walk 25 feet as quickly as possible, but safely. Do not slow down until after you’ve passed the finish line. Ready? Go”. The time was calculated from the initiation of the instruction to start and ends when the patient has reached the 25-foot mark. The task was immediately administered again by having the patient walk back the same distance. Patients were allowed to use assistive devices when doing this task.

The T25-FW is an objective valid assessment of walking disability across a wide range of walking disabilities (Kieseier & Pozzilli, 2012). The T25-FW has an intra-class correlation of >0.8 and is highly reliable (inter-rater ICC 0.942, intra-rater ICC 0.99) (Kieseier & Pozzilli, 2012). It does not exhibit practice effects (Kieseier & Pozzilli, 2012). Twenty percent deterioration in scores indicates a clinically meaningful decrease in gait (Potter et al., 2012; Kieseier & Pozzilli, 2012).

The two minute step test was used to assess aerobic endurance. For this assessment, the subject marched in place with a full step consisting of raising the knee
midway between the patella and the iliac crest. The score was the number of times the right knee reached the required height (Jones & Rikli, 2002).

Rikli & Jones (2012), established a validity coefficient of 0.91 and a test-retest reliability of 0.88 for the 2 minute step test. The 2 minute step test is demonstrated as being a feasible and accurate tool for measuring cardiovascular fitness in older adults (Rikli & Jones, 2012).

*The Timed Up and Go Test (TUG)* was used to assess basic mobility and dynamic balance of the individual by recording the time to stand, walk 3 meters, turn, and walk back to the chair and sit down. A firm chair with arms with a seat height of 46 cm was used, set 3 meters away from a cone. The subject began in the seated position with their back against the chair, arms on the lap, and the feet just behind the distance marker on the floor. The subject was instructed “on the word ‘go’, stand up, walk comfortably and safely to the cone on the floor, walk around the cone, come back, sit all the way back in your chair.” The subject was timed from the word ‘go’ until the subject was back in their seat with their back against the chair. Two practice trials were averaged.

TUG performance time is strongly correlated to the level of functional mobility in the older adult with those completing it in less than 20 seconds were shown to be independent in activities of daily living, and have higher Berg Balance Scores and walk speeds (0.5 m/s) (Shumway-Cook, Brauer, & Woollacott, 2000). Shumway-Cook and colleagues (2000) found that the TUG test had a validity of 87% sensitivity and 87% specificity in older adults. A TUG score of 13.5 seconds or greater in elderly individuals
is correlated to increased risk of falls and has a prediction rate of 90% (Shumway-Cook, Brauer, & Woollacott, 2000). An average score in MS patients is around 13.9 seconds (Potter et al., 2012). Podsiadlo & Richardson (1991) concluded that the TUG test is a valid and reliable test for quantifying functional mobility in elderly individuals with neurological disorders.

**Physiological Variables**

*Blood Pressure* was used to assess the pressure exerted by the circulating blood on the blood vessel walls which was a reflection of cardiovascular health and possibly autonomic nervous system regulation. To measure blood pressure a blood pressure cuff and sphygnanometer were used to detect systolic and diastolic blood pressure. Mean arterial pressure was calculated as diastolic pressure + 1/3 (Systolic pressure – diastolic pressure). Mean arterial pressure reflects the average blood pressure in an individual.

*Body temperature* was recorded tympanically (Braun ThermoScan 5) at the first and last appointment in all participants. In the exercise group, tympanic temperature was measured on the pool deck before exercise, and during the rest period of the 5th interval.

Multiple sclerosis individuals often suffer from an exacerbation of symptoms when body temperature rises. Temperature changes between 0.18 degrees Fahrenheit and 4.14 degrees Fahrenheit have produced exacerbation of symptoms (Peterson, 2001). While these symptoms reverse once the body has cooled, preventing changes in body temperature alleviates these exacerbations. Exercising in an aquatic environment allows
for the added benefit of body heat dissipation at a greater rate than other environments, minimizing heat sensitivity.

Costello and colleagues recommend temperature assessment in MS done with tympanic membrane thermometers for moderate to vigorous activity (Costello, Curtis, Sandel, Bassile, 1996). Tympanic temperature measures are valid measures of brain temperature that reliably reflects core body temperature (Syndulko, Jafari, Woldanski, Baumhefner, & Tourtellotte, 1996).

Cerebral oxygenation was noninvasively measured through Near Infra-Red Spectroscopy (NIRS) which assesses cerebral oxygenation in real time at about 1 cm of cortical tissue (Lintas, Molinari, Simonetti, Franzini, & Liboni, 2013). NIRS is able to quantify the concentrations of oxyhemoglobin and deoxyhemoglobin using multiple wavelengths. In healthy individuals during exercise, cerebral blood flow globally does not change, however local cerebral blood flow increases to the sensorimotor cortex by up to 30% (Ide & Secher, 2000). In MS individuals a hypometabolic component may result from vascular changes (Ge et al., 2009). NIRS measurements have shown that exercise increases oxyhemoglobin, providing for the oxygen needs of the brain tissue, which can be beneficial in MS patients (Rooks, Thom, McCully, & Dishman, 2010).

NIRS recordings were made using a commercially made oximeter (Oxymon MKIII, Artinis Medical Systems, Netherlands). The NIRS probe was secured on the forehead on the midline, 1 cm above the supraorbital ridge similar to as described by Lintas and colleagues (2013). Measurements were taken during the pre and post baseline
measures with the subject seated and eyes closed. Subjects will be asked to rest for 8 minutes while baseline measures were recorded. The last minute of rest with values taken every 5 seconds were averaged to get a resting value. After baseline values were recorded, subjects were asked to open their eyes and a cognitive task was explained (N-back test) during the NIRS measurement. The purpose was to determine if there exist any differences due to a 7 day aquatic aerobic exercise protocol in cerebral oxygenation, cerebral deoxyhemoglobin, % tissue saturation index (%TSI) and total hemoglobin. Because the NIRS does not give an absolute value, changes from baseline to N1 and from baseline to N2 were used to determine if there was a difference from pre-test to post-test for the exercise group compared to the non-exercise group.

Lintas and colleagues (2013) determined NIRS suitable for long term monitoring of the effects on the brain metabolism and vasomotor reactivity and for physiological and neuroscience experimental protocols. Soraghan and colleagues (2008) validated the use of NIRS to measure hemodynamics during cognitive tasks.

The n-Back test is a valid and reliable indicator of working memory (Schmiedek, Lovden, & Lindenberger, 2014). It requires continuous recognition of a stimulus (letter, number or picture) in a particular sequence and the subject must judge whether it matches the one presented n-items ago (Kane, Conway, Miura, & Colflesh, 2007).

**Multiple Sclerosis Self-Efficacy Scale**

Self-efficacy is defined as how the individual perceives their capability in completing a specific task. The scale was developed specifically for Multiple Sclerosis
individuals and contains 18 items that are rated from 10 to 100. Ten corresponds with being uncertain that they are able to perform a specific behavior related to functional independence and psychological management of the disease, whereas 50 is moderately certain and 100 is very certain. The Multiple Sclerosis Self-Efficacy Scale (MSSE) is a validated, reliable and sensitive self-reported measure for measuring self-efficacy in MS patients (Schwartz, Coulthard-Morris, Zeng, & Retzlaff, 1996). Variable assessment is listed in Table 4.

Table 4

<table>
<thead>
<tr>
<th>Variable Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes</td>
</tr>
<tr>
<td>Body Composition: BMI, WHR, Waist Circumference</td>
</tr>
<tr>
<td>25 foot walk test</td>
</tr>
<tr>
<td>2 min step test</td>
</tr>
<tr>
<td>RHR</td>
</tr>
<tr>
<td>Exercise Heart Rate</td>
</tr>
<tr>
<td>BP/MAP</td>
</tr>
<tr>
<td>TUG</td>
</tr>
<tr>
<td>Body Temp</td>
</tr>
<tr>
<td>NIRS</td>
</tr>
<tr>
<td>RPE</td>
</tr>
<tr>
<td>MS Self Efficacy Scale</td>
</tr>
</tbody>
</table>
**Statistical Analysis**

A power analysis to calculate required sample size was completed using pilot data from older adults using a similar aquatic aerobic protocol (Fedor, 2014). The pilot study step test data (mean 14.6 steps, standard deviation 24.5) was used to determine the number of subjects (n=24) required to achieve a power of 0.8 with a Type I error probability at 0.05.

Using IBM SPSS Statistics 20, descriptive measures (age, height, weight, duration of MS, BMI, resting heart rate and resting blood pressure) were compared between the two groups with an independent T-Test. The difference between body composition (waist circumference, waist-to-hip ratio, and BMI) pre-test and post-test values were used to calculate a change score. The exercise group and non-exercise group change scores were compared by using independent samples T-Test. The difference between fitness variables (resting heart rate, heart rate variability, resting blood pressure, mean arterial pressure, 2 minute step test) pre-test and post-test values were used to calculate a change score. The exercise group and non-exercise group change scores were compared using independent samples T-Test. The differences between pre-test and post-test mobility measures (TUG test, and T25-FW test) were used to calculate a change score. The exercise group and control group were compared using independent samples T-Test. The differences between pre-test and post-test cerebral oxygenation (at rest and during cognitive task) were used to calculate a change score. The exercise group and non-exercise group change scores were compared using independent samples T-Test. The
differences between pre-test and post-test MSSE were used to calculate a change score. The exercise group and non-exercise group change scores were compared using independent samples T-Test. Statistical significance was set at $p \leq 0.05$. 
CHAPTER IV
EFFECTS OF A 7 DAY AQUATIC AEROBIC EXERCISE INTERVENTION ON
MOBILITY, FITNESS AND BODY COMPOSITION

Introduction

Multiple sclerosis (MS) is the leading cause of non-traumatic neurologic disability in young adults (Solari et al., 1999). MS is caused by demyelination of axons, focal plaque formation, and inflammation in the central nervous system which results in progressive loss of function. The location of pathology results in varying combinations of symptoms which include fatigue, heat sensitivity, muscle spasms, gait problems and ataxia, dizziness and vertigo, pain, cognitive problems, visual complaints, and bowel and bladder dysfunction (Anthony, Jouria, & Houtman, 2014).

Compounding the impact of the disease, symptoms resulting from MS pathology result in decreased levels of physical activity (Hayes, Gappmaier, & LaStayo, 2011; Marck et al., 2014) and subsequent deconditioning that reduces quality of life (Doring, Pfueller, Paul, & Dorr, 2012). Historically, it was once thought that exercise exacerbated MS symptoms and it was contraindicated in people with multiple sclerosis (Hayes, Gappmaier, & LaStayo, 2011). When exercise increases body temperature, central pathways become blocked producing temporary physical and cognitive symptoms in individuals with MS (Davis, Wilson, White, & Frohman, 2010). Heat sensitivity resulting in worsening symptoms depends on the location of the demyelination and
lesions, and frequently includes deficits in mobility, memory retrieval, processing speed, multitasking, and increased fatigue (Davis, Wilson, White, & Frohman, 2010).

Current research supports the positive effects of exercise in MS treatment, including improved fitness benefits, feelings of well-being, strength and safety of mobility and decreased fatigue (Davis, Wilson, White, & Frohman, 2010, Rietberg, Brooks, Uitdehagg, & Kwakkel, 2011). Exercise also has the capacity to slow disease progression, improves the physiological profile of MS and is well tolerated with a low occurrence of adverse effects (Kargarfard, Etemadifar, Baker, Mehrabi, & Hayatbakhsh, 2012). In addition, Pilutti and colleagues found exercise training is associated with a slight decrease in the risk of relapse when compared to non-exercising MS individuals (Pilutti, Platta, Motl, & Latimer-Cheung, 2014).

The primary aim of rehabilitation in MS individuals is to increase activity levels, as well as their independence (Langdon & Thompson, 1999), by improving mobility (Pilutti, et al., 2011; Kargarfard, Etemadifar, Baker, Mehrabi, & Hayatbakhsh, 2012), improving physical functioning, and easing psychosocial burden (White, Castellano, McCoy, Patel, & Giacobbi, 2012). Molt and Snook (2008) found evidence that physical activity in MS was linked to a greater self-efficacy for function and control, which was also correlated to greater physical and psychological components of quality of life. Self-efficacy is the individual’s perception of his or her capability in completing a specific task, and may play a role in how the individual adjusts to MS symptoms and the psychosocial burden of the disease (Molt & Snook, 2008).
Due to fatigue and overheating issues, MS individuals are generally less physically active than healthy individuals of similar age (Hayes, Gappmaier, & LaStayo, 2011). Heat sensitivity, an increase in body temperature that exacerbates symptoms, affects an estimated 60-80% of MS individuals (Davis, Wilson, White & Frohman, 2010) and is a major barrier to exercise. Worsening of symptoms have been observed with increased body temperature of approximately 0.8°C (Davis, Wilson, White & Frohman, 2010). Aquatic exercise is beneficial in MS individuals because of the ability to transfer body heat to the water 25 times faster than air (Frohman, Okuda, Beh, Treadaway, Mooi, Davis, Shah, Frohman & Frohman, 2015), limiting the increases in body temperature that cause the increase in MS symptoms. In addition, the buoyancy and viscosity of water assists those who have physical weakness (Kargarfard, Etemadifar, Baker, Mehrabi, & Hayatbakhsh, 2012). Aquatic exercise improves neurological functioning, improves activities of daily living (Frohman, Okuda, Beh, Treadaway, Mooi, Davis, Shah, Frohman & Frohman, 2015), reduces joint stress and decreases the fear of falling (Plecash & Leavitt, 2014).

Relapsing Remitting (RRMS) is the most common form of MS, accounting for 85% of Multiple Sclerosis cases (“Types of MS,” n.d.; Berger et al., 2003). RRMS is characterized by exacerbations followed by periods of remission, and is attributed to demyelinating attacks followed by remyelination by the oligodendrocyte (Goldenberg, 2012). Participation in exercise between relapses has the potential to improve gait, mobility, activities of daily living, and quality of life. Several studies have demonstrated
positive effects of exercise on gait parameters and quality of life using four weeks of exercise training. However, no studies to date have used seven consecutive days of exercise (van den Berg et al., 2006; Mostert & Kesselring, 2002), which may be beneficial during times of remission. Previous work, in healthy older adults, showed that both fitness and cognitive parameters were improved with a similar aquatic aerobic exercise protocol in older adults (Fedor, 2014). Therefore, the purpose of this investigation was to determine the potential benefits of seven consecutive days of water-based exercise on mobility, fitness, body composition, and self-efficacy in multiple sclerosis individuals. We hypothesized that a seven day moderate to high intensity water aerobic exercise intervention would improve: 1) mobility as measured through the TUG and T25-FW, 2) cardiovascular fitness by measuring resting heart rate and Two Minute Step Test and 3) self-efficacy using the Multiple Sclerosis Self-efficacy questionnaire. We hypothesized the exercise intervention would not alter body composition (body mass index, waist height ration, Waist circumference) in individuals with MS.

**Methods**

The Kent State University Institutional Review Board approved all experimental protocols. All participants voluntarily signed the written informed consent.

**Participants**

Prospective participants were recruited through a MS study Facebook page, ads in the MS Connector and local newspapers, flyers distributed around town, local MS support groups, and MS special events. Recruiting identified 68 individuals that
expressed interest in the study. These 68 individuals (Figure 2) were prescreened over the phone for inclusion and exclusion criteria, and explained the details of the study. Twenty-one individuals, (3 males and 18 females) were interested and eligible for this investigation. Participants were excluded if they were pregnant or at risk for becoming pregnant, had psychiatric illness, had a history of non-MS related neurological disorder or injury, had current or past history of drug or alcohol abuse, had a history of learning disorder or developmental disability, or had sensory function that impaired cognitive testing. In addition, all participants were diagnosed with MS by a physician, were between 20-65 years of age, and had physician approval for the study. All participants were English speaking.

![Figure 2. Recruitment and allocation of participants in MS study](image)

**Figure 2.** Recruitment and allocation of participants in MS study
Experimental Protocol

Participants arrived at their scheduled time for the pre-test at the Kent State University Exercise Physiology laboratory. After reviewing and signing the written informed consent, anthropometric measurements including height, weight, and hip and waist circumference were collected. Participants were fitted with a Polar heart rate monitor (RS800CX) which was used to assess resting heart rate. Body temperature was taken tympanically using a Braun Thermoscan 5. Resting blood pressure was recorded and mean arterial pressure, body mass index (BMI) and waist-to-hip ratio (WHR) were calculated. The participants then completed a series of tests including the two minute step test, twenty-five foot walk test, and timed up and go test (TUG). The two minute step test was administered by having the participant march in place for two minutes following the protocol by Jones & Rikli (2002). The distance midway between the patella and the iliac crest was measured and then marked on the wall. The score was determined by the number of times the right knee reached the required height. The 25 foot walk (T25-FW) test was given by instructing the participant to walk as quickly but as safely as possible the length of 25 feet. The time was recorded from the word “Go” until the participant passed the 25-foot mark. The participant then completed a second trial of the same task immediately by having them walk back the same distance. Participants were allowed to use assistive devices while completing the T25-FW and the TUG test. Participants used the same assistive device for the post-test. The timed up and go test (TUG) (Podsiadlo & Richardson, 1991) was administered by having the
participant start in the seated position, hands on their lap, back against the chair. On the word “go” they were instructed to stand up, walk quickly but safely to the cone on the floor, walk around the cone, come back and sit in the chair. The cone was placed at 3 meters and the timer was stopped when they were seated with their back against the chair.

After each participant completed the mobility, fitness, and body composition measures, they were given the Multiple Sclerosis Self–Efficacy questionnaire (MSSE), a self-reported measure. The MSSE is composed of 2 parts, 9 questions assessing function and 9 questions assessing control. Each question was weighted at 100 points, with a total of 900 points from each section. The function questions seek to determine the participant’s sense of confidence that they can perform behaviors that allow them to engage in daily living activities. The control questions assess the level of confidence that MS individuals can control their symptoms and their reactions to disease related limitations and the impact of the disease on life activities. A total score was determined by combining the two sections together for a total of 1800 possible points. Higher scores indicate higher self-efficacy (Riazi, Thompson, & Hobart, 2004). The post-test was given on day 9 and mirrored the pretest protocol.

**Non-exercise Participants**

Participants in the non-exercise group were asked to maintain their current lifestyle during the 7 days between the pre-test and post-test. They were instructed to continue their usual activities of daily living, and were asked not to start a new exercise program during the study.
Exercise Participants

The day following the pre-test, participants were asked to attend morning exercise sessions every day for the next 7 days. Small groups of participants (2-5) performed aquatic aerobic interval style exercise lead by a certified special population aquatic aerobics instructor. The aerobics group was monitored by a lifeguard and by at least two trained research staff. Individuals were encouraged to maintain their target training intensity between 65-75% of their maximal heart rate as calculated through the Karvonen formula (Karvonen, Kentala, & Mustala, 2007). Heart rate and rate of perceived exertion (RPE) were monitored every nine minutes throughout the exercise protocol. The exercise protocol provided one minute of rest between four minute segments of exercise allowing for recovery time between the exercise bouts (Table 5). The eight exercise intervals rotated between upper body, lower body or total body exercise. For safety, participants were required to rest if their heart rate was greater than 75% of their calculated maximal heart rate or RPE greater than 17. The participant was able to return to exercise when they reached 65% of their calculated maximal heart rate or RPE was at 13.
Table 5

Aquatic Aerobic Exercise Protocol

<table>
<thead>
<tr>
<th>Protocol Interval</th>
<th>Time</th>
<th>Subjects will be performing</th>
<th>Target HR/RPE</th>
<th>Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-exercise</td>
<td>As subjects trickle in</td>
<td>On Pool deck prior to aquatic exercise</td>
<td></td>
<td>Tympanic temperature, RPE, HR</td>
</tr>
<tr>
<td>Warm Up</td>
<td>0-10 min</td>
<td>Walking and stretching in water</td>
<td>30-40% Age Adjusted Max Heart Rate</td>
<td>At end of warm up RPE and HR</td>
</tr>
<tr>
<td>Exercise</td>
<td>Measure at the 2nd, 4th, 6th and 8th rest period (every 9 minutes)</td>
<td>Minutes 10-50-Cardiovascular endurance and strength training and range of motion exercises for upper and lower body intervals 8 X 4 min intervals with 1 minute rest</td>
<td>65-75% Age Adjusted Max Heart Rate If heart rate is greater than 75% AAMHR, or RPE greater than 17, the subject must rest at the side of the pool while being monitored by the researcher. The subject may return to exercise when the heart rate is at 65%, or RPE is at 13. The subject will be closely monitored with additional heart rate checks (every 5 minutes) as needed.</td>
<td>RPE and HR at each rest period, every 9 minutes Tympatic Temperature at 40 min only</td>
</tr>
<tr>
<td>Cool Down</td>
<td>50-60 minutes</td>
<td>Walking and stretching in water</td>
<td>30-40% Age Adjusted Max Heart Rate</td>
<td>RPE and HR</td>
</tr>
<tr>
<td>Post exercise</td>
<td>As they come out of pool</td>
<td>On Pool Deck after aquatic exercise</td>
<td>Heart rate must be below 40% age adjusted max heart rate in order to remove the heart rate monitor and go home.</td>
<td>HR, RPE</td>
</tr>
</tbody>
</table>

Statistical Analysis

The exercise and non-exercise group’s baseline measures were compared using independent samples T-tests. All measures for mobility, fitness, body composition, and self-efficacy were compared by calculating a change score, then comparing the two groups using independent samples T-tests. The change score was determined by subtracting the pre-test scores from the post-test scores for each variable. Mobility was
measured through TUG and T25FW, and cardiovascular fitness was assessed through resting heart rate, resting blood pressure, mean arterial pressure, two minute step test. Anthropometric measures included waist circumference, waist-to-hip ratio and BMI, and weight. Self-efficacy was measured through the Multiple Sclerosis Self-Efficacy questionnaire (MSSE). The MSSE consisted of two sections (control and function) which were analyzed independently and then together for a total score. Statistical significance was set at $p \leq 0.05$. Effect size for the mobility, fitness, body composition, and self-efficacy variables was calculated through Cohen’s $d$. Cohen’s $d$ less than or equal to 0.2 represents a small effect size, 0.5 a moderate effect size, and 0.8 a large effect size.

**Results**

Twenty-one individuals with twelve participants in the exercise group (9 females, 3 males) and nine participants in the non-exercise group (9 females) completed the study. Recruiting began in January 2015 and continued through September 2015. Participants were allocated to the exercise and non-exercise group based on a combination of random assignment and convenience sampling, depending on their availability for pool exercise. The aquatic exercise protocol was offered based on pool availability between 8am -10am for each of the 4 exercise sessions; and to consistently offer morning exercise to minimize the possibility of fatigue which often increases throughout the day.

There were no significant differences (Table 6) between the exercise and non-exercise groups in age, disease duration, years of education, the resting heart rate, systolic
blood pressure, diastolic blood pressure, mean arterial pressure, temperature, 2 minute step test, TUG test, T25-FW, waist circumference, hip circumference, waist-to-hip ratio, and height. The exercise group had a significantly higher BMI and weight compared to the non-exercise group.
Table 6

*Descriptive Statistics*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Exercise (n=12)</th>
<th>Non-exercise (n=9)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.9 ± 9.3</td>
<td>51.1 ± 7.2</td>
<td>0.634</td>
</tr>
<tr>
<td>Disease Duration</td>
<td>14.1 ± 9.2</td>
<td>12.6 ± 7.2</td>
<td>0.679</td>
</tr>
<tr>
<td>Years of Education</td>
<td>13.9 ± 1.9</td>
<td>14.8 ± 4.3</td>
<td>0.589</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>70.8 ± 11.7</td>
<td>75.6 ± 11.4</td>
<td>0.359</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>128.6 ± 16.8</td>
<td>117.3 ± 12.5</td>
<td>0.107</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>74.3 ± 9.7</td>
<td>78.4 ± 9.2</td>
<td>0.339</td>
</tr>
<tr>
<td>Mean Arterial Pressure</td>
<td>92.3 ± 9.7</td>
<td>91.3 ± 9.4</td>
<td>0.814</td>
</tr>
<tr>
<td>Temperature (°F)</td>
<td>97.7 ± 0.5</td>
<td>97.3 ± 0.8</td>
<td>0.210</td>
</tr>
<tr>
<td>2 Minute Step Test (# of steps)</td>
<td>55.8 ± 21.5</td>
<td>48.8 ± 35.3</td>
<td>0.581</td>
</tr>
<tr>
<td>TUG Test (seconds)</td>
<td>15.8 ± 14</td>
<td>15.1 ± 10.4</td>
<td>0.896</td>
</tr>
<tr>
<td>T25-FW (seconds)</td>
<td>9.9 ± 8.6</td>
<td>9.8 ± 7.9</td>
<td>0.978</td>
</tr>
<tr>
<td>Waist Circumference (cm)</td>
<td>101.7 ± 15.7</td>
<td>90.0 ± 10.4</td>
<td>0.067</td>
</tr>
<tr>
<td>Hip Circumference (cm)</td>
<td>113.0 ± 13.0</td>
<td>103.7 ± 7.6</td>
<td>0.054</td>
</tr>
<tr>
<td>Waist-to-hip Ratio</td>
<td>0.9 ± 0.09</td>
<td>0.87 ± 0.06</td>
<td>0.345</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>65.08 ± 2.74</td>
<td>65.29 ± 4.51</td>
<td>0.904</td>
</tr>
<tr>
<td>Weight (lbs)</td>
<td>182.3 ± 36.8</td>
<td>150.7 ± 24.4</td>
<td>0.038*</td>
</tr>
<tr>
<td>BMI</td>
<td>30.2 ± 6.6</td>
<td>24.9 ± 2.7</td>
<td>0.023*</td>
</tr>
</tbody>
</table>

Values represent mean ± standard deviation, *- statistically significant differences
Exercise Variables

The exercise group worked during the intense exercise intervals at 53.7% of ± 10.11 age predicted maximal heart rate. Their RPE ranged from 8-17 with a mean of 10.8 ± 2.24. The exercise protocol required individuals to rest if their heart rate was greater than their target heart rate (65-75% maximal heart rate) which was calculated through the Karvonen formula (Karvonen, Kentala, & Mustala, 2007), or a RPE greater than 17. None of the individuals in the exercise group reported an RPE above 17 or exhibited a heart rate above their calculated target heart rate. The mean body temperature was 97.8 ± 0.95 degrees Fahrenheit during the exercise intervals.

Mobility Measures

Mobility was assessed through the TUG and T25-FW (exercise n=11, non-exercise n=9). One participant’s data was removed from analysis for the TUG Test, T25-FW, and 2 Minute Step test due to their extremely high level of disability which was greater than any other individuals.

In the individual analysis of Timed up and Go (TUG), improvement was defined as scores below zero, whereas decreases in performance on the TUG test were defined as scores above zero. It is interesting to note that 82% (9/11 individuals, Figure 3) of the exercise participants improved their TUG test performance, while only 66% (6/9 individuals, Figure 4) of the non-exercise group showed improvement. It is also important to note that while the non-exercise group were fairly consistent in their pre-test and post-test scores, the individuals in the exercise group showed changes in both
directions. However, when the change score from pre- to post intervention means were calculated, there were no significant (p=0.567, d = 0.269) differences detected between the two groups (Figure 5).

![Exercise TUG Test](image)

*Figure 3. TUG test individual performance of exercise group (n=11)*
Figure 4. TUG test individual performance of participants in the non-exercise group (n=9)

Figure 5. Mean change score and standard deviation of TUG test (p=0.567) for the exercise (-1.04 ± 2.60, n = 11) and non-exercise (-0.463 ± 1.56, n=9) groups
In the T25-FW, the exercise group (-0.90 seconds) improved with a slightly faster time compared to the control group (+0.11 seconds) which maintained their performance. In the exercise group, 73% (8/11 individuals, Figure 6) improved their T25-FW performance while only 11% (1/9 individuals, Figure 7) in the non-exercise group showed improvement.

*Figure 6. Individual data of T25-FW for the exercise group (n=11)*
Figure 7. Individual data of T25-FW for the non-exercise group (n=9)

The mean change scores of T25-FW showed no significant differences between the exercise and non-exercise groups (Figure 8, p = 0.139, d = 0.702).

Figure 8. Average change scores (p=0.139) for the T25-FW for the exercise group (-0.905 ± 1.54, n=11) and non-exercise group (0.106 ± 1.33, n=9)
Cardiovascular Fitness

Cardiovascular fitness was measured through the resting heart rate measure and the 2 minute step test. Pre-test and post-test resting heart rate values were plotted as individual data for the exercise group (n=12) in figure 9 and in the non-exercise group (n=9) in figure 10.

*Figure 9.* Individual data of exercise group for resting heart rate (n = 12)
There were no significant differences ($p = 0.498, d = 0.312$, Figure 11) between the two groups for change in resting heart rate. The average resting heart rate increased by 2.7 bpm in the exercise group compared to the non-exercise group which demonstrated a decreased in resting heart rate by 0.44 bpm.
Figure 11. Mean change scores ($p=0.498$) of heart rate for the exercise ($2.67 \pm 11.36$, $n=12$) and non-exercise groups ($-0.44 \pm 8.37$, $n=9$)

The individual data for the two minute step test of the exercise group ($n=11$, figure 12) showed that 73% (8/11) of participants increased in the number of steps at the post-test. Sixty-two percent (5/8) of the non-exercise group ($n=8$, figure 13) demonstrated an increased number of steps. One exercise participant was excluded to level of disability that prevented completing the tests, while one participant from the non-exercise group was excluded due to measurement error.
Figure 12. Individual data of the exercise group (n=11) 2 minute step test

Figure 13. Individual data of the non-exercise group (n=8) 2 minute step test
There were no significant differences (p = 0.275, d = 0.528, Figure 14) between the exercise and the non-exercise group on the change score for the 2 Minute Step Test. The exercise group completed about 8 more steps than the non-exercise group.

![Change in 2 Minute Step Test Score](image)

*Figure 14. Average change scores (p=0.275) for the 2 minute step test in the exercise group (12.455 ± 15.36, n=11) and non-exercise group (4.50 ± 14.90, n=8)*

The diastolic blood pressure trended toward significant differences (p = 0.054, d = 0.922) between the groups in which the exercise group (6.67 ± 13.71, n = 12) increased by about 7 mmHg at the post-test, whereas the non-exercise group (-4.67 ± 10.68, n=9) decreased by approximately 5 mmHg at the post-test. There were no significant changes in the two groups (exercise 2.50 ± 13.24, n = 12, non-exercise -4.11 ± 5.71, n = 9) after the exercise intervention for systolic blood pressure (p = 0.178, d = 0.648). There were no significant differences between the exercise (3.19 ± 7.90, n = 12) and non-exercise group (-2.26 ± 12.09, n = 9) for mean arterial pressure (p=0.226, d=0.534).
**Anthropometric Results**

There were no significant differences in weight, BMI, waist circumference, or waist to hip ratio between the exercise and non-exercise groups as a result of the exercise intervention (Table 7).

Table 7

*Average Change Scores of Anthropometric Variables in the MS Exercise and Non-exercise Group.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Exercise (n=12)</th>
<th>Non-exercise (n=9)</th>
<th>p-Value</th>
<th>Effect Size d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>-0.14±1.68</td>
<td>-1.17±2.03</td>
<td>0.216</td>
<td>0.556</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.08±0.55</td>
<td>0.11±0.60</td>
<td>0.435</td>
<td>0.347</td>
</tr>
<tr>
<td>Waist Circumference</td>
<td>0.37±2.92</td>
<td>0.06±6.06</td>
<td>0.878</td>
<td>0.065</td>
</tr>
<tr>
<td>Waist to Hip Ratio</td>
<td>0.01±0.02</td>
<td>0.00±0.07</td>
<td>0.782</td>
<td>1.93</td>
</tr>
</tbody>
</table>

Values represent mean ± standard deviation, *- statistically significant differences

**Self-Efficacy Results**

There were no significant differences between the two groups at baseline for MSSE Function (exercise 660.0 ± 318.21, n = 12, non-exercise 747.5 ± 159.44, n = 8), MSSE Control (exercise 640.0 ± 175.34, n = 12, non-exercise 617.5 ± 266.64, n = 8), or MSSE Total (exercise 1387.5 ± 288.20, n = 12, non-exercise 1277.5 ± 532.72, n = 8). There were no significant differences for MSSE Function (*p* = 0.380, *d* = 0.386), MSSE Control (*p* = 0.623, *d* = 0.225) or Total MSSE (*p* = 0.624, *d* = 0.216) between the exercise and non-exercise group in self-efficacy after 7 days of aquatic exercise (Figure 15). One
individual in the non-exercise group did not complete the MSSE for the pre-test, and was removed from analysis.

**Figure 15.** Average change scores for the MSSE in the exercise (MSSE Control 62.50 ± 68.24, MSSE Function 37.50 ± 91.37, MSSE Total 100.00 ± 123.83, n=12) and non-exercise group (MSSE Control 46.25 ± 75.77, MSSE Function 88.75 ± 164.18, MSSE Total 135.00 ± 194.79, n=8)

**Clinically Meaningful Differences**

Coleman and colleagues suggest a clinically meaningful difference in the 25 foot walk test is demonstrated by at least a 20% improvement from the pre-test to the post-test (Coleman, Sobieraj, & Marinucci, 2012). In this study, the exercise group improved by 12%. Though falling below the clinically meaningful threshold of 20%, a trend of 12% improvement in the exercise group compared to the less than 1% improvement in the non-exercise group, holds potential that brief aquatic exercise can improve mobility in
MS. This is further supported by the moderate to large effect size for the 25 foot walk test.

Foley and colleagues determined that minimal clinically important differences (MCID) could be calculated for the TUG test by taking the mean value of the pre-assessment and multiplying by 15% (Foley, Barnes, Hasson, 2015). The results fall below the minimal clinically important differences (Table 8), however, there is a trend toward improvement shown in the exercise group that is not shown in the non-exercise group, with a small effect size present.

Table 8

*Determining Clinically Significant Differences*

<table>
<thead>
<tr>
<th>Test</th>
<th>Exercise Group</th>
<th>Non-Exercise Group</th>
<th>Effect Size</th>
<th>Standard of Clinically Significant</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 Foot Walk</td>
<td>Improved by 12%</td>
<td>Decrease by &lt; 1%</td>
<td>Moderate to large</td>
<td>20% improvement (Coleman and colleagues, 2012)</td>
</tr>
<tr>
<td>TUG</td>
<td>Improved by 9%</td>
<td>3% improvement</td>
<td>Small</td>
<td>15% improvement from pre-test (Foley and colleagues, 2015)</td>
</tr>
<tr>
<td>2 Minute Step</td>
<td>Increased # steps by 21%</td>
<td>Increase # steps by 18%</td>
<td>Moderate</td>
<td>No standard found in literature Fedor, 2015 showed 12.3 % improvement with an exercise intervention in elderly individuals</td>
</tr>
</tbody>
</table>

**Discussion**

This study showed that a short duration, moderately intense, aquatic exercise intervention can produce small changes in mobility, fitness, and self-efficacy in Multiple Sclerosis individuals. There were no adverse events or heat induced MS symptoms.
during the exercise sessions. These results extend the conclusions of Snook and Motl (2009), which found that exercise training programs are associated with small clinically meaningful improvements in mobility of walking in MS individuals. There were no statistically significant differences between the two groups for mobility, cardiovascular fitness, or self-efficacy. Body composition was also analyzed, and as expected, changes did not occur within the short intervention.

The exercise group demonstrated that sixteen percent more individuals improved in the TUG test than in the non-exercise group. TUG mimics activities of daily living such as rising and lowering from a chair and maneuvering to turn around. In the T25-FW, greater improvements were shown as 62% more individuals in the exercise group had a faster time than in the non-exercise group. Fitness also demonstrated an increase of 11% more exercise individuals improving in the number of steps compared to the non-exercise group, with exercise participants taking on average 8 more steps than those in the non-exercise group.

Land based exercise has been shown to produce benefits in MS individuals such as improvements in mobility and balance (Lord, Wade, & Halligan, 1998) however, aquatic exercise is favorable in MS for a variety of reasons. Aquatic exercise reduces heat induced symptoms and stress on joints, reduces the risk of falls during exercise, increases range of motion, and accommodates a variety of disability levels found in MS. This study demonstrated the safety, benefits, and feasibility of aquatic exercise in MS individuals.
The individual data for mobility and fitness often showed a mix of increases and decreases in measures for the exercise group indicating the diversity of the disease process and response to the exercise intervention. Participants were diverse in their MS type, symptoms (fatigue, pain, spasm) and disability level, and this may have contributed to the heterogeneous results found in each of the variables and their response to exercise. The non-exercise group individual measures remained more consistent from pre-test to post-test showing little change.

Participants in the exercise and non-exercise group did not differ in age, disease duration, years of education, fitness, mobility, or body temperature. However, the exercise group had a significantly higher BMI and body weight, which may partially be explained by the inflexible exercise schedule. In order to participate in the exercise group, individuals had to be available at the exercise time (8 am, seven days consecutively) which conflicted with some participants’ work schedules. Kahraman and colleagues researched determinants of physical activity in MS and found an association of decreased physical activity with unemployment (Kahraman, Savci, Coskuner-Poyraz, Ozakbas, Idiman, 2015). Those with more flexible schedules were more likely to participate in the exercise session which may have correlated with decreased employment and decreased physical activity, and increased BMI.

Mobility

Mobility is an important function of daily living, and this study aimed to determine if 7 days of consecutive aquatic exercise in MS individuals could improve
mobility. Improvements in mobility were defined by a faster time to perform the TUG test or T25-FW at the post-test compared to the pre-test. We hypothesized that there would be improvements in mobility in the exercise group, and the non-exercise group would not change from baseline. This study demonstrated small changes that showed improvements in the TUG test and T25-FW in the exercise group.

Latt and colleagues showed an increase in risk of falls in individuals who took greater than 12 seconds to complete the TUG test (Latt, Lord, Morris, & Fung, 2009). Using this as a general estimate of disability, it was noted that one participant in the exercise group performed the TUG test at 103.89 seconds at the post-test, qualitatively indicated that he was exhausted from the exercise and was the most disabled in the study. This individual was removed from the analysis for the TUG test, T25-FW, and the 2 minute step test due to high level of disability.

The TUG test mirrors tasks of daily living, including getting up from a seated position, maneuvering around a cone, and sitting down. Both groups improved in TUG time, but at the post-test, the exercise group (1.04 seconds faster) showed greater improvements than the non-exercise group (0.46 seconds faster). Additionally, 82% (9/11 individuals) of the exercise group improved their TUG time where as 66% (6/9 individuals) of the non-exercise group showed improvements in the TUG time.

The individual data of the TUG test in the non-exercise group shows minimal changes from the pre-test to the post-test, whereas the exercise group TUG test individual data shows a mix of individual’s increasing, decreasing and not changing performance
time from pre to post after the exercise intervention. Statistically the mean between the two groups is very similar, but the response to exercise is different. It is likely that with the wide range of symptoms and disability resulting from the diverse focal lesion location severity, and diversity of symptoms (fatigue, pain, spasticity) found in persons with MS, individuals respond differently to the exercise intervention.

This study showed small improvements in the exercise group (-0.90 seconds) in the T25-FW, while the non-exercise group (+.11 seconds) exhibited a slightly slower performance. In the T25-FW, 73% (8/11 individuals) of the exercise group compared to 11% (1/9 individuals) in the non-exercise group showed improvements. Similar results were determined through a four week treadmill aerobic intervention by Van den Berg and colleagues who found improved gait speed (van den Berg, Dawes, Wade, Newman, Burridge, Izadi, & Sackley, 2006). The exercise intervention was 30 minutes of walking at 55-85% age adjusted maximal heart rate three times a week. They also found that four weeks after the exercise, walking performance returned towards baseline, indicating a need for continued exercise. Similarly, Marinho-Buzelli and colleagues used aquatic therapy in 20 MS individuals and demonstrated a fair ability to improve gait speed (Marinho-Buzelli, Bonnyman, & Verrier, 2014).

Fatigue may have affected performance in mobility measures in the exercise group. The post-test was given the day immediately following the last day of exercise, and participants verbally indicated that they were exhausted. The T25-FW, TUG test and 2 minute step test were given consecutively in a random order, and the individuals
identified when they felt rested enough to perform each test. It may have been more beneficial to incorporate a 15 minute rest between each of these tests; which is similar to the protocol followed by Kahraman and colleagues (2015). It also may have been beneficial to administer the post-test following 24 hours of rest.

**Fitness**

Similar to mobility, fitness levels can impact functions of daily living, and the aim of this study was to determine if 7 days of consecutive aquatic exercise would improve cardiovascular fitness in multiple sclerosis individuals. We hypothesized that there would be an improvement in the exercise group in fitness variables (2 minute step test, resting heart rate, and blood pressure) while the non-exercise group was expected not to significantly change from their pre-test values.

In the step test, the exercise group increased by a mean of 12.5 steps and 73% (8/11) of the individuals showed improvements. The non-exercise group improved by a mean of 4.5 steps, and 62.5% (5/8 individuals) increased their number of steps. One individual was removed from the non-exercise group analysis due to error in recording her number of steps. One individual was removed from the analysis of the exercise group because of their high level of disability.

Similarly, Mostert and Kesselring (2002) showed that after a cycling exercise intervention people with MS had a normal cardiovascular response to exercise, though they have a low anaerobic threshold, low maximal volume of oxygen, and high energy consumption compared to healthy individuals. They found greater fitness improvements
in semi-ambulatory individuals compared to ambulatory individuals. Rampello and colleagues (2007) used a progressive aerobic 8 week intervention in mild to moderate disability MS individuals and found improvements in aerobic fitness, walking distance and speed. Rampello and colleagues suggested that the mixed results found in MS exercise intervention studies may be a result of the varying degree of disability in people with MS and the length of training periods. In the current study the wide range of disability levels and fatigue may have impacted performance on the mobility and fitness measures.

Multiple studies have produced improved results in mobility, endurance, strength, and balance in MS individuals (Hayes, Gappmaier, & LaStayo, 2011, Cakit and colleagues, 2010, Carter and White, 2003). In addition, O’Connell and colleagues (2003) found improved fitness, pre and post heart rate, gait cadence and RPE without a change in gait speed in a 12 week aerobic exercise intervention. Exercise in MS has been shown to be feasible and safe, and produce a variety of positive health outcomes.

The mixed heart rate and blood pressure responses were diverse in both groups, reflecting the complexity of autonomic dysfunction in individuals with MS. The cardiovascular autonomic dysfunction that can occur in MS depends on the lesion load and location in the brain and spinal cord and is correlated with disease activity and progression of disability (Flachenecker, Reiner, Krauser, Wolf, Toyka, 2001). Both parasympathetic and sympathetic nervous system dysfunction has been noted in MS individuals (Sternberg, 2015). We hypothesized that resting heart rate would decrease
with increased fitness due to the exercise intervention. However, this study showed the exercise group’s resting heart rate increased 2.7 bpm compared to the non-exercise group which decreased by 0.44 bpm. It is not likely that fitness declined over the course of the week of exercise; but if the individuals had decreased vagal tone, the exercise intervention may have increased parasympathetic activity. It is uncertain if this is the case or if the sympathetic nervous system increased response because the underlying cardiovascular dysfunction was not determined for each individual in this study.

Heart rate is regulated through the parasympathetic nervous system and may improve function with lower intensity, longer duration exercise. For example, Goit, Paudel, Khadka, Roy and Shrewastwa (2014) found that 6 months of mild to moderate intensity exercise decreased sympathetic activity while increasing parasympathetic activity. MS individuals who have decreased vagal tone may benefit from this type of exercise. Mostert and Kesselring demonstrated no changes in heart rate over 4 weeks of cycling exercise (2002).

Blood pressure was hypothesized to improve due to the exercise intervention in the exercise group with little change expected in the non-exercise group. This study showed that blood pressure did not significantly improve, but trended toward higher systolic, diastolic and mean arterial pressure values. The sympathetic branch of the nervous system regulates short term and long term blood pressure through the hormone norepinephrine. People with MS have been found to have low sympathetic function
which can present as inflammation, neurodegeneration, and chronic cerebrospinal venous insufficiency (Sternberg, 2012).

The effects of exercise on the autonomic nervous system have been shown to depend on the intensity, duration, and mode of exercise (Sternberg, 2015). In MS individuals undergoing short high intensity aerobic exercise (86-93% maximal heart rate), improvements in sympathetic nervous system function were recorded. The resulting decreases in systolic blood pressure after one hour of exercise lasted for 24 hours (James, Muson, Maldonado-Martin, & De Ste Croix, 2012). Lima and colleagues had similar observations when using high intensity resistance training in MS individuals (Lima, Forjaz, Silva, Meneses, Siva, & Ritti-Dias, 2011). This type of exercise may be used to improve sympathetic function in MS individuals.

Increases in diastolic blood pressure and mean arterial pressure were shown in the current study, indicating that the intensity level and duration may not have been sufficient to improve the sympathetic nervous system response, and a reflection of the autonomic dysfunction found in MS individuals.

**Exercise Heart Rate, RPE and Temperature**

The participants in the exercise group were encouraged to work between 65-75% of maximal heart rate as calculated by the Karvonen Method (Karvonen, Kentala, &Mustala, 2007). Researchers attempted to encourage participants to increase intensity from the pool deck by performing the exercises along with the participants, verbally
encouraging them, and providing quick upbeat workout music in the genera they preferred.

During the exercise session the mean heart rate during the exercise interval was 53.7% of maximal heart rate. Most participants had difficulty increasing their heart rate to the target range, which may be a result of problems with balance and equilibrium, and autonomic dysfunction. Several days of adjustment to the aquatic environment led to lower intensity levels in the first few days of exercise. The last four days of exercise participants worked at an average of 56% ± 9.6 maximal heart rate and an RPE of 11.2 ± 2.7. While Mostert & Kesselring (2002) found MS individuals unable to stress the cardiovascular system maximally, MS participants were able to reach 75-80% of their maximal heart rate during a cycling protocol. The heart rate values in this group ranged from 107-114 bpm, however this was accomplished by programming the training heart rate into a Cardiotrainer® bicycle ergometer, which in turn achieved the training heart rate by automatically adjusting the work load.

It is unclear if heart rate and the Borg RPE scale of 20 accurately reflect exercise intensity in people with multiple sclerosis, as they have a higher heart rate reserve (Mostert & Kesselring, 2002), and lower ability to stress the cardiovascular system. In this study, RPE’s slowly increased over the workout session; however the workout heart rates did not reflect this increase (Appendix 5). In addition, the workout RPE averaged 10.8 ± 2.2, indicating that either the MS participants could not reach the desired intensity or RPE was not an accurate reflection of intensity. The interval style work out
incorporating a 1 minute rest between 4 minutes of exercise may have prevented the heart 
rate from reaching the target intensity. Using the Borg 10 scale of RPE may have been a 
better reflection on intensity and has been validated in the MS population by Morrison, 
Cooper, White, Larson, Leu, Zaldivar, & Ng, 2008).

Individuals with multiple sclerosis may have a more difficult time of improving 
fitness due to pathogenic factors altering the body’s response to exercise. A similar 
exercise intervention protocol of continuous aquatic aerobic exercise in healthy elderly 
people revealed improvements in fitness (Fedor, 2014) which was not demonstrated in 
the MS population. The MS participants verbally expressed that they were fatigued from 
the consecutive days of exercise which may have impacted their performance on the post-
test fitness and mobility tests. Including a day of rest between the last day of exercise 
and the post-test may have allowed recovery time needed to improve performance on the 
fitness and mobility measures.

Aquatic exercise increases the ability to use the body’s buoyancy in water to 
allow for longer physically active periods due to decreased gravity. However, the 
reduced effect of weight bearing and weight shifting in the water compared to land may 
have decreased the cardiovascular impact of the exercise session. Due to the large 
variety of fitness and disability level in the group, some participants had to balance more 
poolside, decreasing their intensity level during the aquatic aerobic exercise. In addition, 
the variability of symptoms in people with MS may have contributed to symptoms that
could impact the individuals performance in the water (pain, balance, spasticity), and thereby making it more difficult for them to achieve their target intensity level.

A major challenge is the increase in MS symptoms when body temperature rises, especially with exercise. Aquatic exercise was chosen due to the ability to help MS individuals regulate body temperature. In this study, the mean body temperature prior to exercise was 97.3 °F and during the exercise intervals was 97.8 °F. Participants did not indicate any increase in symptoms during the exercise intervention. The pool temperature was 85 degrees Fahrenheit. This study reinforced that aquatic exercise is beneficial and viable in the MS population.

**Body Composition**

It was hypothesized that the exercise protocol, due to its short duration, would not alter body composition. No changes in body composition, as measured through BMI, Waist-Hip-Ration (WHR), and waist circumference, were exhibited. Waist and hip circumferences were both taken over the individual’s base clothing. If there was any outerwear, they were asked to remove it. Measuring the hip and waist circumference in this way made the individuals more comfortable, but decreased the accuracy of the measure. Consistency in measuring technique was kept from the pre-test to the post-test.

**Self-Efficacy**

Self-efficacy is a person’s perception of their capability in completing a specific task. Exercise is known to improve self-efficacy, and this study aimed to determine if a short 7 day aquatic exercise intervention would improve self-efficacy in MS individuals.
We hypothesized that self-efficacy would improve in the exercise group with no changes in the non-exercise group. The Multiple Sclerosis Self-Efficacy Questionnaire (MSSE) has two components, one on function and one on control. Nine questions determine a person’s sense of confidence that they can perform behaviors that allow them to engage in daily living activities (function). A second section of nine questions assesses control or the confidence that they can control their symptoms, reactions to disease related limitations, and the impact of the disease on life activities.

This study showed that both groups increased in self-efficacy (for function, control, and total self-efficacy) from the pre-test to the post-test. It is probable that taking the MSSE a second time in such a short span of time, individuals were more confident and comfortable which may have increased their self-efficacy scores. Participants also had less anxiety at the post-test because they knew where to go to reach the exercise physiology lab, already knew the researchers, and knew what to expect from the testing protocol. The exercise group was fatigued at the post-test which may have impacted their MSSE scores. In the exercise group, 92% (11/12) of individuals improved in their total self-efficacy scores, while 75% (6/8) of the non-exercise group individuals improved. Both groups improved by 75% (9/12 in the exercise group; 6/8 in the non-exercise group) for self-efficacy of control. For self-efficacy of function, 67% (8/12) individuals in the exercise group showed improvements compared to 62.5 % (5/8) individuals in the non-exercise group.
Exercise may have produced a greater self-efficacy of control, or the perception that the individual can manage their MS symptoms. This is compared to the perception that the individual can perform functional activities of daily living, in which the exercise group did not improve as much in. The fatigue resulting from the 7 days of consecutive exercise may have impacted participant’s outlook on how they are able to perform their daily tasks. Separating the post-test from the last day of exercise by 24 hours of rest may have been beneficial in controlling for the effects of fatigue. Finally, the exercise intervention may not have been long enough to elicit changes in self-efficacy.

**Limitations and Future Direction**

The study was limited by the number of participants recruited. Recruiting consisted of a convenience sample that introduced differences between the groups that could have been controlled for through complete random sampling. Offering the exercise session at different times may be beneficial in allowing those with work schedules to participate in the exercise intervention; however fatigue in MS typically increases throughout the day. The level of disability, daily physical activity level, depression and fatigue should be determined in order to identify covariates. Future studies may need to incorporate 24 hours of rest between the last day of exercise and the post-test to reduce the impact of fatigue. A rest period of 15 minutes between the fitness tests also should be incorporated to minimize the effects of fatigue.

Multiple Sclerosis individuals have cardiovascular autonomic dysfunction, and it is unclear if heart rate and RPE are good measures of intensity level. The participants in
This study were encouraged to exercise at their target heart rate level, but most participants had a difficult time reaching their calculated intensity. It is estimated that cardiovascular autonomic dysfunction occurs in 19-42% of MS individuals, and the symptoms include fatigue and orthostatic challenges (Racosta, Sposato, Morrow, Cipriano, Kimpiski, & Kremenchutzky, 2015). This is due to the variability of lesions in the brain stem and spinal cord.

Sternberg suggests that mild to moderate aerobic exercise may be beneficial in patients who have decreased vagal activity; while short bursts of high intensity exercise may help those who have low sympathetic function (2015). Further investigation is needed on detecting autonomic dysfunction and validated means of monitoring intensity level in this population. Clinically it would be beneficial to determine the effects of different exercise protocols on the autonomic nervous system in MS individuals.

If the MS exercise participants were working at 53% of their calculated maximal heart rate, the intensity level may be too low to elicit mobility, fitness and self-efficacy changes in 7 days of exercise. Future studies could increase the days of exercise sessions or the intensity level.
CHAPTER V

THE EFFECTS OF AEROBIC EXERCISE ON CEREBRAL OXYGENATION IN MULTIPLE SCLEROSIS USING NEAR INFRA-RED SPECTROSCOPY

Introduction

Multiple Sclerosis (MS) affects 2.1 million individuals worldwide (Dibble, Lopez-Lennon, Lake, Hoffmeister, & Gappmaier, 2013). MS is caused by demyelination of axons, focal plaque formation, and inflammation in the central nervous system which results in progressive loss of function. In addition, MS has hypometabolic pathology consisting of decreased oxygen utilization and decreased absolute cerebral blood flow (Sun, Tanaka, Kondo, Okamoto, & Hirai, 1998; Brooks, et al., 1984). Reduced cerebral oxygen metabolism (Sun, Tanaka, Kondo, Okamoto, & Hirai, 1998; Brooks et al., 1984), and mitochondrial damage have been found in MS individuals (Ge et al., 2009).

Positron emission tomography (PET) examination revealed a decreased brain oxygen utilization and extraction present in MS accompanied by extensive reduction in cerebral glucose metabolism (Brooks and colleagues, 1984). Bakshi and colleagues (PET scan) demonstrated hypometabolic activity in the cerebral cortex, subcortical nuclei, supratentorial white matter, and infratentorial structures (Bakshi, Miletich, Kinkel, Emmet, & Kinkel, 1998). Sun and colleagues (1998) found that as disability increased, oxygen metabolism decreased, which was also correlated with cognitive impairment. The level of cerebral hypometabolism was also correlated to the number of relapses.

MS is recognized as a diffuse global brain pathology that has a major vascular impact (Ge et al., 2009). During normal functioning, metabolic gas exchange at the brain
capillary level extracts oxygen from hemoglobin resulting in deoxyhemoglobin with four unpaired electrons (Ge et al., 2009). In MS individuals, the oxygen extraction is diminished which also reduces deoxyhemoglobin that is detected in the venous network (Ge et al., 2009). In addition to reduced oxygen to the brain tissues, Ge and colleagues (2009) also found cerebral chronic venous insufficiency in MS individuals with venous visibility negatively correlated to lesion load. Widespread decreases in brain venous blood deoxyhemoglobin levels reflect the cerebral hypometabolic picture in MS (Ge et al., 2009). Ge and colleagues (2009) found decreased visibility of periventricular white matter venous vasculature in MS subjects when compared to healthy controls. The proposed mechanism is two-fold: a decrease in oxygen utilization in tissue and a decrease in glucose utilization in cortico-cerebral metabolism that is correlated with lesion load (Ge et al., 2009; Blinkenberg et al., 2000).

Near Infra-Red Spectroscopy (NIRS) can be used to noninvasively measure cerebral oxygenation in real time at about 1 cm of cortical tissue (Lintas, Molinari, Simonetti, Franzini, & Liboni, 2013). NIRS is used to quantify the absolute concentration changes of total, oxyhemoglobin and deoxyhemoglobin using multiple wavelengths, expressed in arbitrary units. Though cerebral blood flow in healthy individuals globally doesn’t change, local cerebral blood flow can increase to the sensorimotor cortex by up to 30% during exercise (Ide & Secher, 2000). NIRS measurements have shown that exercise increases oxyhemoglobin, providing for the
oxygen needs of the brain tissue, which can be beneficial in MS patients (Rooks, Thom, McCully, & Dishman, 2010).

Compounding the impact of the disease, symptoms resulting from MS pathology are correlated with decreased levels of physical activity (Hayes, Gappmaier, & LaStayo, 2011; Marck et al., 2014) and subsequent deconditioning that reduces quality of life (Doring, Pfueller, Paul, & Dorr, 2012). Exercise has the capacity to slow disease progression, improves the physiological profile of MS, and is well tolerated with a low occurrence of adverse effects (Kargarfard, Etemadifar, Baker, Mehrabi, & Hayatbakhsh, 2012).

Prakash and colleagues discovered a positive correlation between higher fitness and gray matter volume, higher scores on composite measures of information processing speed, and an inverse relationship with brain tissue damage in MS (Prakash, Snook, Motl, & Kramer, 2010). The authors concluded that fitness exerts a prophylactic influence on cerebral atrophy that occurs early in the disease process, thereby, preserving neuronal integrity in MS and reducing long-term disability.

MS individuals can benefit specifically from aquatic exercise because water conducts heat 25 times faster than air, (Frohman et al., 2015). Heat sensitivity occurs in 60-80% of MS individuals (Anthony, Jouria, & Houtman, 2014), and is caused when nerve conduction becomes blocked to central pathways as core body increases (Davis et al., 2008; Humm et al., 2004; Frohman et al., 2013). The result is a transient increase in MS symptoms with exercise; and the water’s ability to dissipate body heat aids in
minimizing core temperature increase and associated heat related symptoms (Kargarfard, Etemadifar, Baker, Mehrabi, & Hayatbakhsh, 2012).

Aquatic exercise is recommended by the American Physical Therapy Association in treatment of Multiple Sclerosis (Kargarfard, Etemadifar, Baker, Mehrabi, & Hayatbakhsh, 2012). Aquatic exercise provides several benefits including buoyancy and viscosity of water that assists MS individuals who have physical weakness (Kargarfard, Etemadifar, Baker, Mehrabi, & Hayatbakhsh, 2012). Water immersion increases pressure in the lower body, causing blood to be diverted to the thoracic area, placing the heart under an increased workload (Chu, Rhodes, Taunton, & Martin, 2002). The increased pressure also increases the workload of the lungs by as much as 60% (Agostoni, Gurtner, Torri, & Rahn, 1966). Aquatic therapy also reduces joint stress and decreases the fear of falling (Plecash & Leavitt, 2014).

The improved metabolic profile that results from exercise can impact MS pathology. Several studies have described the hypometabolic impact of MS (Fan et al., 2015; Sun, Tanaka, Kondo, Okamoto, & Hirai, 1998; Brooks et al, 1984; Kidd et al. 1999; Bakshi, Miletich, Kinkel, Emmet, & Kinkel, 1998). However only one study has used Near Infrared Spectroscopy Systems (NIRS) to monitor cerebral oxygenation levels in MS (Lintas, Molinari, Simonetti, Franzini, & Liboni, 2013). There are no studies to date that have used NIRS to determine the impact of exercise on cerebral oxygenation in MS, though exercise has the potential to increase oxygenation through increased blood flow and improved oxygen utilization (Ide & Secher, 2000; Rooks, Thom, McCully,
Dishman, 2010). Lintas and colleagues (2013) determined NIRS suitable for long term monitoring of the effects on the brain metabolism and vasomotor reactivity and for physiological and neuroscience experimental protocols. Soraghan and colleagues validated the use of NIRS to measure hemodynamics during cognitive tasks (Soraghan, Matthews, Markham, Pearlmutter, O’Neill, & Ward, 2008). We hypothesized that a seven day water aerobic exercise intervention would improve cerebral oxygenation as measured through Near Infrared Spectroscopy (NIRS) in individuals with MS.

**Methods**

The Kent State University Institutional Review Board approved all experimental protocols. All participants voluntarily signed the written informed consent.

**Participants**

Participants were recruited through flyers placed in neurological clinics, local MS support groups, local businesses, MS special events, and ads in local papers and the MS Connector. Sixty-eight individuals expressed interest in the study, and were prescreened for inclusion and exclusion criteria (figure 22). Twenty-one individuals (3 males and 18 females) were eligible and interested in the study. Participants were excluded if they: were pregnant or at risk for becoming pregnant, had psychiatric illness, had a history of non-MS related neurological disorder or injury, had current or past history of drug or alcohol abuse, had a history of learning disorder or developmental disability, or had sensory function that impaired cognitive testing. In addition, all participants were diagnosed with MS by a physician, were between 20-65 years of age, and had physician approval for the study. All participants were English speaking.
**Experimental Protocol**

Participants arrived at their scheduled time for the pre-test at the Kent State University Exercise Physiology Laboratory. After reviewing and signing the written informed consent, anthropometric measurements including height, weight, and hip and waist circumference were collected.

**Near Infra-Red Spectroscopy**

Cerebral oxygenation was noninvasively measured using Near Infra-Red Spectroscopy (NIRS). NIRS recordings were made using a commercially made oximeter (Oxymon MKIII, Artinis Medical Systems, Netherlands). The NIRS probe was secured on the right forehead on the midline, 1 cm above the supraorbital ridge similar to as described by Lintas and colleagues (2013). Measurements were taken during the pre and...
post baseline measures with the subject seated and eyes closed. Subjects were asked to rest for 8 minutes while baseline measures were recorded. The last minute of rest with values taken every 5 seconds were averaged to get a resting value.

After baseline values were recorded, subjects were asked to open their eyes while a cognitive task was explained (N-back test). Participants played the N-1 back game (Brain Workshop version 4.8.4) three times, each game lasting about 65 seconds. The researcher then explained the N-2 back game, and participants played it three times using the same software. The last minute (the third game) of the N-1 and the last minute (the third game) of the N-2 were each averaged to determine a N-1 score and N-2 score. The N-Back test is a valid and reliable indicator of working memory (Schmiedek, Lovden, & Lindenberger, 2014). It requires continuous recognition of a stimulus (letter, number or picture) in a particular sequence and the subject must judge whether it matches the one presented n-items ago (Kane, Conway, Miura, & Cofles, 2007).

The purpose was to determine if there were differences due to a 7 day aquatic aerobic exercise protocol in cerebral oxygenation, cerebral deoxyhemoglobin, % tissue saturation index (%TSI) and total hemoglobin. Because the NIRS does not give an absolute values for oxyhemoglobin, deoxyhemoglobin, and total hemoglobin; changes from baseline to N1 and from baseline to N2 were used to determine if there was a difference from pre-test to post-test for the exercise group compared to the non-exercise group. TSI was normalized as a percentage and a change score from pre-test to post-test was used to report changes.
Non-exercise Participants

Participants in the non-exercise group were asked to maintain their current lifestyle during the 7 days between the pre-test and post-test. They were instructed to continue their usual activities of daily living, and were asked not to start a new exercise program during the study.

Exercise Participants

The day following the pre-test, participants were asked to attend morning exercise sessions every day for the next 7 days. A certified special population aquatic aerobics instructor led the exercise session. Small groups of participants (2-5) were monitored by a lifeguard and at least two trained research staff during the 60 minute exercise sessions. The individual target training intensity (65-75% of their maximal heart rate) was calculated through the Karvonen formula (Karvonen, Kentala, &Mustala, 2007). Heart rate and rate of perceived exertion (RPE) were monitored every 9 minutes throughout the exercise protocol. The exercise protocol provided one minute of rest between four minute segments of exercise allowing for recovery time between the exercise bouts (Table 8). The eight exercise intervals rotated between upper body, lower body or total body exercise. For safety, participants were required to rest if their heart rate was greater than 75% of their calculated maximal heart rate or RPE greater than 17. The participant was able to return to exercise when they reached 65% of their calculated maximal heart rate or RPE was at 13.
Table 9

Aquatic Exercise Procedure

<table>
<thead>
<tr>
<th>Protocol Interval</th>
<th>Time</th>
<th>Subjects will be performing</th>
<th>Target HR/RPE</th>
<th>Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-exercise</td>
<td>As subjects trickle in</td>
<td>On Pool deck prior to aquatic exercise</td>
<td>30-40% Age Adjusted Max Heart Rate</td>
<td>Tympanic temperature, RPE, HR</td>
</tr>
<tr>
<td>Warm Up</td>
<td>0-10 min</td>
<td>Walking and stretching in water</td>
<td>65-75% Age Adjusted Max Heart Rate</td>
<td>At end of warm up RPE and HR</td>
</tr>
<tr>
<td>Exercise</td>
<td>Measure at the 2nd, 4th, 6th and 8th rest period (every 9 minutes)</td>
<td>Minutes 10-50-Cardiovascular endurance and strength training and range of motion exercises for upper and lower body intervals 8 X 4 min intervals with 1 minute rest</td>
<td>If heart rate is greater than 75% AAMHR, or RPE greater than 17, the subject must rest at the side of the pool while being monitored by the researcher. The subject may return to exercise when the heart rate is at 65%, or RPE is at 13. The subject will be closely monitored with additional heart rate checks (every 5 minutes) as needed.</td>
<td>RPE and HR at each rest period, every 9 minutes Tympanic Temperature at 40 min only</td>
</tr>
<tr>
<td>Cool Down</td>
<td>50-60 minutes</td>
<td>Walking and stretching in water</td>
<td>30-40% Age Adjusted Max Heart Rate</td>
<td>RPE and HR</td>
</tr>
<tr>
<td>Post exercise</td>
<td>As they come out of pool</td>
<td>On Pool Deck after aquatic exercise</td>
<td>Heart rate must be below 40% age adjusted max heart rate in order to remove the heart rate monitor and go home.</td>
<td>HR, RPE</td>
</tr>
</tbody>
</table>

Statistical Analysis

Descriptive measures (age, height, weight, duration of MS, BMI, resting heart rate, mean arterial pressure, and resting blood pressure) were compared between the exercise and non-exercise groups using an independent T-test (IBM SPSS Statistics 20).

For % TSI, mean change scores from post-test to pre-test were calculated and an
independent samples T-test was used to determine significant differences between the exercise and non-exercise groups. The quantification of oxyhemoglobin, deoxyhemoglobin, and total hemoglobin concentrations were expressed in arbitrary units. To standardize the data, change scores were calculated by taking the change from N1 to baseline, and from N2 to baseline for each test. Repeated measures were used to determine differences from the pre-test and post-test between the two groups. Statistical significance was set at $p \leq 0.05$.

**Results**

Twenty-one individuals, (86% female) completed the study. Twelve individuals were allocated to the exercise group, and nine to the non-exercise group through convenience sampling. The exercise intervention took place between eight and ten in the morning for seven consecutive days, which was not feasible for some individuals due to work schedules. These individuals were placed in the non-exercise group. There were no significant differences (Table 9) between the exercise and non-exercise groups in age, disease duration, years of education, the resting heart rate, systolic blood pressure, diastolic blood pressure, or mean arterial pressure.
Table 10

*Descriptive Statistics of MS Participants*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Exercise (n=12)</th>
<th>Non-exercise (n=9)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.9 ± 9.3</td>
<td>51.1 ± 7.2</td>
<td>0.634</td>
</tr>
<tr>
<td>Disease Duration</td>
<td>14.1 ± 9.2</td>
<td>12.6 ± 7.2</td>
<td>0.679</td>
</tr>
<tr>
<td>Years of Education</td>
<td>13.9 ± 1.9</td>
<td>14.8 ± 4.3</td>
<td>0.589</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>70.8 ± 11.7</td>
<td>75.6± 11.4</td>
<td>0.359</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>128.6± 16.8</td>
<td>117.3 ±12.5</td>
<td>0.107</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>74.3 ± 9.7</td>
<td>78.4 ± 9.2</td>
<td>0.339</td>
</tr>
<tr>
<td>Mean Arterial Pressure</td>
<td>92.3± 9.7</td>
<td>91.3 ± 9.4</td>
<td>0.814</td>
</tr>
</tbody>
</table>

Values represent mean ± standard deviation, *- statistically significant differences

The Exercise Intervention

During the exercise intervals, the exercise group worked at an intensity of 53.7 % ± 10.1 of their age predicted maximal heart rate. RPE for the group ranged from 8-17 with a mean of 10.6 ± 2.2. The participants HR and RPE did not reach above their target heart rate (65-75% maximal heart rate) which was calculated through the Karvonen formula, or a RPE greater than 17; therefore none of the participants were required to stop exercise to lower their intensity level as a safety precaution. In general, participants took several days to adapt to the exercise intervention, and an average of the last four days of exercise intensity was 56% ± 9.6 maximal heart rate, and an RPE of 11.2 ± 2.7.
The mean body temperature was 97.8 degrees Fahrenheit during the exercise intervals. The exercise protocol was safe and feasible for this group.

**Tissue Saturation Index (TSI)**

Due to measurement error, four individuals from the exercise group and 3 from the non-exercise group were excluded from analysis. Mean change scores for percent TSI were calculated by subtracting the pre-test value from the post-test values to determine a change score. An independent sample T-test was used to determine if there were differences between the two groups. Though there were no statistically significant differences (Table 10) between the two groups, the exercise group showed 3.29% greater improvements at rest than the non-exercise group (Figure 23).

Table 11

*Mean Change Scores % TSI.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Exercise (n=8)</th>
<th>Non-exercise (n=6)</th>
<th>p-Value</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>% TSI rest mean change score</td>
<td>4.27±14.5</td>
<td>0.98±17.2</td>
<td>0.704</td>
<td>0.207</td>
</tr>
<tr>
<td>% TSI N1 mean change score</td>
<td>4.39±22.66</td>
<td>3.74±26.47</td>
<td>0.961</td>
<td>0.026</td>
</tr>
<tr>
<td>% TSI N2 mean change score</td>
<td>2.91±23.54</td>
<td>0.17±10.92</td>
<td>0.797</td>
<td>0.150</td>
</tr>
</tbody>
</table>

Values represent mean ± standard deviation, *- statistically significant differences
Figure 17. Mean change scores for % TSI. The exercise group showed greater improvements at rest, during the N1 task, and during the N2 task.

Individual data for oxyhemoglobin, deoxyhemoglobin, and total hemoglobin were standardized by calculating the change from resting to the N1 cognitive task. The same was done from resting to the N2 cognitive task. A repeated measures analysis was then used to determine if there were differences between the exercise and non-exercise group.

**Oxyhemoglobin**

No significant differences between the change of pre-oxyhemoglobin N1 cognitive task to baseline and post-oxyhemoglobin N1 to baseline (p=0.992) or from pre-oxyhemoglobin N2 to baseline and post-oxyhemoglobin to baseline (p=0.734) were found (Table 11). Both groups increased in oxyhemoglobin at the pre-test and post-test (figure 24). An increase in oxyhemoglobin and total hemoglobin indicate increase blood flow.
Figure 18. Change in Oxyhemoglobin from N1 to Baseline and N2 to Baseline in Exercise (n = 12) and Non-exercise (n=9) Groups

Table 12

Change from Baseline to the Cognitive Task for Oxyhemoglobin, Deoxyhemoglobin, and Total Hemoglobin

<table>
<thead>
<tr>
<th>Variable</th>
<th>Exercise (n=12) Mean ± SD</th>
<th>Non-exercise (n=9) Mean ± SD</th>
<th>p value (time × condition)</th>
<th>Effect Size $\eta^2_p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxy N1-baseline</td>
<td>Pre-test 1.18 ± 2.59</td>
<td>Post-test 0.933 ± 1.25</td>
<td>Pre-test 1.26 ± 1.95</td>
<td>Post-test 1.00 ± 1.28</td>
</tr>
<tr>
<td>Oxy N2-baseline</td>
<td>1.23 ± 2.21</td>
<td>1.39 ± 1.41</td>
<td>1.30 ± 1.42</td>
<td>1.06 ± 1.82</td>
</tr>
<tr>
<td>Deoxy N1-baseline</td>
<td>-0.33 ± 0.58</td>
<td>-0.19 ± 0.51</td>
<td>-0.11 ± 0.69</td>
<td>-0.38 ± 1.31</td>
</tr>
<tr>
<td>Deoxy N2-baseline</td>
<td>-0.44 ± 0.62</td>
<td>-0.16 ± 0.94</td>
<td>-0.42 ± 0.58</td>
<td>-0.61 ± 1.66</td>
</tr>
<tr>
<td>Total N1-baseline</td>
<td>0.85 ± 2.67</td>
<td>0.74 ± 1.18</td>
<td>1.15 ± 1.92</td>
<td>0.62 ± 1.81</td>
</tr>
<tr>
<td>Total N2-baseline</td>
<td>0.71 ± 2.25</td>
<td>1.15 ± 1.65</td>
<td>0.88 ± 1.39</td>
<td>0.45 ± 3.00</td>
</tr>
</tbody>
</table>

Values represent mean ± standard deviation, *- statistically significant differences
**Deoxyhemoglobin**

An increase in deoxyhemoglobin indicates improved oxygen utilization.

Deoxyhemoglobin decreased in both groups, however, the exercise group showed smaller decreases after the exercise intervention (Figure 25). The exercise group improved by 0.14 micromol/liter of tissue while the non-exercise group further decreased deoxyhemoglobin by 0.27 micromol/liter of tissue from the pre-test to the post-test for the N1 to baseline change. For the N2 to baseline change, the exercise group showed an improvement in deoxyhemoglobin by 0.28 micromol/liter of tissue from the pre-test to the post-test while the non-exercise group further decreased 0.19 micromol/liter of tissue. The changes of deoxyhemoglobin N1 to baseline (p=0.434) and deoxyhemoglobin N2 to baseline (p = 0.359) were not significant (Table 11).

![Deoxyhemoglobin chart](image)

*Figure 19. Change in Deoxyhemoglobin from N1 to Baseline, and from N2 to Baseline for the Exercise (n=12) and Non-exercise (n=9) Groups*
**Total Hemoglobin**

Both groups increased in total hemoglobin across the conditions (Figure 26), though the change in total hemoglobin N1 to baseline (p = 0.108) and N2 to baseline (p = 0.402) were not significant (Table 11). For the change in total hemoglobin from N1 to baseline, both groups showed less of an increase at the post-test compared to the pre-test. The exercise group showed 0.11 micromol/liter of tissue less increase, and the non-exercise group showed 0.53 micromol/liter of tissue less increase at the post-test compared to the pre-test. For the change in total hemoglobin from N2 to baseline, the exercise group improved by 0.44 micromol/liter of tissue from the pre-test to the post-test while the non-exercise group decreased from the pre-test by 0.43 micromol/liter of tissue.

![Total Hemoglobin Chart](chart.png)

*Figure 20. Changes in Total Hemoglobin from N1 to Baseline and N2 to Baseline for the Exercise (n=12) and Non-exercise (n=9) Groups*
Discussion

It was hypothesized that the 7 day aerobic exercise protocol would improve cerebral oxygenation in the exercise group, but not in the non-exercise group. While there were no statistically significant differences between the exercise and non-exercise groups for %TSI, oxyhemoglobin, deoxyhemoglobin or total hemoglobin there were small clinically meaningful improvements that exhibited as increases in oxyhemoglobin and total hemoglobin, representing increased blood flow. In the change from N2 to baseline for total hemoglobin, the exercise group showed an increase in 0.44 micromol/liter of tissue. The deoxyhemoglobin also decreased by a smaller amount after the exercise intervention in the exercise group compared to the non-exercise group, representing and improved oxygen utilization.

The % Tissue Saturation Index (%TSI) reflects the change in concentration of oxygenated and deoxygenated hemoglobin, and is an estimate of the oxygen saturation in the tissue. The mean change scores in %TSI show that the exercise group showed greater improvements in %TSI than the non-exercise group. This indicates a greater extraction of oxygen to the tissues after the aerobic exercise intervention, which is beneficial in the MS population.

MS exhibits a hypometabolic component to the disease process. Two proposed mechanisms are that brain tissues are extracting a decreased amount of oxygen, and there is a decrease in vascular function (Sun, Tanaka, Kondo, Okamoto, & Hirai, 1998;
Brooks, et al., 1984). The resulting decrease in glucose utilization in the cortico-cerebral metabolism is correlated to increased lesion load (Blinkenberg et al., 2000).

While MS individuals’ exhibit decreased oxygen utilization, exercise has been shown to improve the aerobic system (Mostert & Kesselring, 2002). Aerobic exercise increases peak oxygen uptake in MS individuals (Hayes, Gappmaier & LaStayo, 2011). Exercise in MS promotes growth factors stimulating cell proliferation, synaptic plasticity, neuroprotection, and neurogenesis (Doring, Pfueller, Paul, & Dorr, 2012). While the improvements in TSI are small, it is exciting that a short exercise intervention can benefit the oxygen utilization in MS individuals, and increases the need for further study on longer duration exercise, mode of exercise (high intensity training vs long duration aerobic training), and greater intensity level.

**Oxyhemoglobin**

This study aimed to determine the response of cerebral oxygen at rest and during a cognitive task after a 7 day aquatic exercise intervention. We hypothesized that oxyhemoglobin would progressively increase as the cognitive tasks became more difficult, and that oxyhemoglobin would increase more in the exercise group compared to the non-exercise group at the post-test compared to the pre-test. This study showed that oxyhemoglobin increased during the cognitive tasks in both groups. There was a smaller increase in both groups at the post-test from baseline to N1 cognitive task possibly indicating that oxygen demands were increased greater than to delivery. It is also probable that individuals were not cognitively working as hard to complete the task
because they were already familiar with it from the pre-test. The change from baseline to N2 was greater in the post-test than in the pre-test for the exercise condition reflecting a more efficient capacity to respond to oxygen demands and a greater blood flow with a more difficult cognitive task.

Ide and Secher (2000) showed an increase in regional cerebral uptake of oxygen during exercise in healthy individuals. Obrig and colleagues demonstrated cerebral oxygen exceeds the increase in oxygen demand in motor stimulation as shown with increased oxyhemoglobin (Obrig, Hirth, Junge-Hulsing, Doge, Wolf, Dirnagl, & Villringer, 1996). Increase oxyhemoglobin and total hemoglobin suggest increases in blood volume which correlate to cerebral blood flow (Sakatani, Lichty, Xie, Li, & Zuo, 1999). Furthermore, cerebral activation, including cognitive tasks, increases cerebral blood flow, thereby increasing cerebral oxygenation. Most of the hemoglobin determined by NIRS is post-cellular, after the cells have extracted oxygen (Ide & Secher, 2000). Oxyhemoglobin remaining in the blood post-cellular suggests the ability to exceed oxygen demand.

Rooks and colleagues completed a review on healthy individuals and found that during low to moderate intensity aerobic exercise (<60% VO₂ max), there were moderate to large increases in the prefrontal cortex for oxyhemoglobin, deoxyhemoglobin and blood volume (as estimated by total hemoglobin) (Rooks, Thom, McCully, & Dishman, 2010). They further found that aerobically trained individuals had a higher oxyhemoglobin, deoxyhemoglobin and total hemoglobin level at hard intensities.
compared to untrained individuals. In addition, a common pattern including a rise in oxyhemoglobin, deoxyhemoglobin and total hemoglobin during moderate to hard intensities, which fell at very hard intensities; with training status influencing the response. As very hard intensities were reached, the body’s capacity to keep up with oxygen demands was reduced. MS individuals, though generally deconditioned, respond to exercise similarly to healthy individuals, and may benefit from improved oxygenation resulting from exercise.

Sakatan and colleagues (1999), suggested that decreased oxyhemoglobin and total hemoglobin indicate a decreased cerebral blood flow during cognitive tasks. Their study compared young adults to aged adults. The most common pattern for both groups was an increase in oxyhemoglobin, increased total hemoglobin and a decreased deoxyhemoglobin. However, in aged adults there was a significant difference in these patterns as more aged adults demonstrated a decrease in oxyhemoglobin and total hemoglobin compared to the younger adults suggesting a decrease in regional cerebral blood flow. With already compromised oxygenation, MS individuals may follow a similar response to aging, and exercise potentially can improve the metabolic profile.

While the differences between the two groups comparing the pre-test to the post-test are not significant, the trend toward improved efficiency of the body to supply oxygen demands could be very beneficial in the hypometabolic condition of MS. Increased duration or intensity may further improve cerebral oxygenation.
Deoxyhemoglobin

Deoxyhemoglobin reflects the tissue’s ability to extract oxygen. As oxygen is extracted, deoxyhemoglobin increases. While differences were not statistically significant, both groups exhibited decreases in deoxyhemoglobin in all conditions, however, the exercise group had less of a decrease than the non-exercise group. This suggests an improved ability to utilize oxygen due to the exercise intervention. It is possible that MS individuals have a decreased cerebral blood oxygen reservoir due to decrease vasculature, causing a diminished ability to improve oxyhemoglobin. However, the exercise group exhibited an improved oxygen utilization as reflected by the improved deoxyhemoglobin from pre-to-post exercise. The non-exercise group continued to decrease in deoxyhemoglobin, decreasing oxygen utilization.

Total Hemoglobin

Differences between the two groups in total hemoglobin were not statistically significant. Total Hemoglobin mirrored a similar pattern to the oxyhemoglobin. Changes in total hemoglobin reflect changes in blood volume, and is correlated with cerebral blood flow (Sakatani, Lichty, Xie, Li, & Zuo, 1999). In the N2 cognitive task, the exercise group increased total hemoglobin which was also demonstrated with oxyhemoglobin. Possibly an increase in blood flow due to the exercise intervention improved the capacity to distribute oxygen to the tissues.
Limitations and Future Direction

This study has several limitations, the first being that the exercise intervention may not have been long or intense enough to elicit significant changes in %TSI, oxyhemoglobin, deoxyhemoglobin, or total hemoglobin. In addition, the sample size was small, and recruiting more participants would have been beneficial. Due to a limited response to recruiting and pool scheduling, the participants were assigned to each group based on their ability to attend the exercise protocol and if the number of individuals in that testing session was large enough for an exercise session. The pool exercise was also an interval style workout; a completely aerobic protocol may have produced greater improvements. The NIRS only measures in arbitrary units, limiting the ability for comparisons pre-to-post-test. Finally, the N1 and N2 back cognitive tasks were difficult cognitive tests. Participants who had a hard time with the N1 task may have been less motivated to try harder for the N2 task.

Future research is required to determine the details of the hypometabolic component in MS and to determine how MS individuals respond to exercise including longer duration and higher intensity protocols. Determining the impact of aerobic, high intensity training, or resistance training on cerebral oxygenation may provide an optimal training mechanism during the window between relapses.
CHAPTER VI
SUMMARY

MS individuals comprise a unique population because of the diversity of pathology and symptoms. The location of demyelination and lesions in the central nervous system determine what symptoms the individual will experience, and result in individuals that are less physically active and deconditioned. Though the symptoms often prevent MS individuals from exercising, exercise is safe, feasible, and often providing benefits that counteract the pathology. Aquatic exercise in particular is beneficial because of ability of the water to absorb body heat, minimizing the symptoms that increase transiently during exercise due to increased core temperature. In addition, aquatic exercise provides an environment that decreases joint stress, reduces risk of falls, and allows for a wide range of disability levels which was helpful in this study due to the diversity of disability levels of the participants.

While disappointing, this study did not show any statistically significant results for improvements in mobility, fitness, body composition, self-efficacy, or cerebral oxygenation; it did provide insight to how MS individuals respond to short duration exercise. The trends demonstrated through this study encourage MS individuals to exercise, even if only short windows exist between relapses, and provide peace of mind that exercise is safe, feasible, beneficial and desirable.

This study revealed small improvements that can impact functions of daily living and quality of life in MS individuals. Mobility, an important function of living improved
in 73% (8/11) of the exercise participants compared to 11% (1/9) of the non-exercise participants, as measured through the twenty-five foot walk test. Similar improvements were demonstrated in fitness as measured by the two minute step test. Improved fitness usually correlates with decreased resting heart rate and blood pressure, however the exercise participants exhibited an increase in resting heart rate, while the non-exercise group had a slight decrease. Blood pressure followed the same pattern, which reflects the autonomic dysfunction in MS. Demyelination and lesions can impact the parasympathetic (controlling HR) and sympathetic (controlling BP) responses, and exercise may have been beneficial in stimulating both of these parts of the nervous system resulting in an increased response in HR and BP. Self-efficacy also improved in both groups, though the differences were not significant.

This study also showed that the short exercise intervention produced small changes in cerebral oxygenation, with greater improvements in the exercise group at post-test in the harder cognitive task. Total hemoglobin also followed this pattern indicating an increased cerebral blood flow during the harder cognitive tasks. Increased deoxyhemoglobin indicates increased oxygen extraction. Both groups decreased in deoxyhemoglobin, the exercise group showed less decrease after the exercise intervention while the non-exercise group showed a further decrease in deoxyhemoglobin from the pre-test to the post-test. The exercise group was more efficient at extracting oxygen during the cognitive tasks than the non-exercise group, though the differences were still not significant.
This study is not without limitations. The sample size was very small, and participants were very diverse in their disability, symptoms, and disease duration. The sample should have been randomly assigned to the exercise and non-exercise conditions; instead participants were assigned by convenience sampling. Increasing the exercise intensity, decreasing the number of rest periods between intervals, and lengthening the exercise duration to greater than one week may also be beneficial. Allowing for 24 hours of rest post exercise may have enhanced performance on fitness, mobility and self-efficacy measures as fatigue most likely impacted the results. Including 15 minutes of rest between the tests may also have been beneficial. It was also unclear if HR and RPE accurately reflected the exercise intensity levels in MS.

Future direction includes determining the optimal time of exercise that allows benefits between relapses. In addition, determining modes (high intensity training, low intensity aerobic training, resistance training), intensities, and durations of exercise that can positively impact the autonomic function in MS. Exercise can influence the autonomic nervous system, so prescribing exercise for the desired effect (parasympathetic vs sympathetic stimulation) individually would be beneficial for people with MS. Along with this, developing tools that give insight to the autonomic dysfunction and allow for monitoring would allow a more purposeful exercise paradigm to be prescribed. It is also important to have tools that accurately reflect intensity levels in MS so that the exercise can be monitored accordingly, therefore, validating RPE and HR as intensity measures in MS would be beneficial.
APPENDICES
APPENDIX A

INFORMED CONSENT FORM
Appendix A

Informed Consent Form

Informed Consent to Participate in a Research Study

Study Title: Exercise and Cognition in Multiple Sclerosis

Principal Investigator: Mary Beth Spitznagel, PhD

Co-Investigators: Angela Ridgel, PhD; Jennifer Petersen, MS; Dayana Calvo, BA

You are being invited to participate in a research study. This consent form will provide you with information on the research project, what you will need to do, and the associated risks and benefits of the research. Your participation is voluntary. Please read this form carefully. It is important that you ask questions and fully understand the research in order to make an informed decision. You will receive a copy of this document to take with you.

Purpose: The purpose of this study is to better understand the relationship between exercise and thinking skills in people diagnosed with Multiple Sclerosis. To do this, we are asking people to participate in testing of thinking skills and physical abilities. Some people will be randomly assigned to a 1 week-long, daily water aerobics exercise program, while others will not. We will look at how thinking skills and physical abilities change during this time period, and how participation in the exercise program may affect these changes.

Procedures: If you decide to take part in this study, you will first be asked to complete a series of tests. These evaluations will include:

Tests of thinking skills: You will be asked to complete a short set of pen/paper and question/answer tests that assess your ability to focus and sustain your attention, learn and remember new information, and other types of thinking skills. These tests will take about 45-60 minutes.

Questionnaires: You will also be asked to complete paper-and-pencil questionnaires. The questions ask about your personal characteristics (such as health issues) as well as your exercise habits, mood, symptoms of pain and fatigue self-efficacy, and how all of these affect your day to day life. The questionnaires will take about 20-30 minutes.
**Physiological Testing**: Baseline levels of your height, weight, and waist to hip ratio will be recorded today. Heart rate, blood pressure, tympanic body temperature, and cerebral oxygenation will also be recorded. These tests will take about 10 minutes.

**Functional Testing**: You will be asked to perform some functional testing to determine your fitness level. These tests will assess your cardiovascular fitness, and mobility. These tests will take about 45-60 minutes.

**Activity Monitoring**: You will be asked to wear an activity monitor daily throughout the study. The monitor can be worn on your wrist, waistband, shirt, or in your pocket throughout the day.

Once you have completed the evaluations, you will be randomly assigned to either the Exercise Group or the No Exercise Group.

If you are assigned to the No Exercise Group, you will be asked only to complete the above baseline testing, and repeat these tests one week later, making no other changes to your normal routine.

If you are assigned to the Exercise Program, you will be asked to attend daily exercise sessions for 7 days. Sessions are 60 minutes each day, and consist of a structured program of water aerobic exercises. The specific intensity of the exercise will depend upon your age and fitness level, and will be determined by the project investigators based upon your physical testing. Target heart rates will be monitored with heart rate monitors and used to measure exercise intensity. Research assistants will be poolside during the course of the exercise class to monitor your heart rate and observe for any signs of physical distress. **You will not be allowed to exercise to exhaustion.**

**Benefits**: Both the exercise and control group will benefit from information given to them regarding the cognitive function testing and baseline fitness testing. For the exercise group, your involvement in this study may provide cognitive benefits to you, as prior work shows that even one week of exercise can improve thinking skills. You may also experience other benefits associated with exercise, such as improved fitness, health, and quality of life. The outcome of the research will provide important information on the relationship between exercise and thinking skills in people diagnosed with Multiple Sclerosis.

**Risks and Discomforts**: We believe that the risks of this study are minimal. One risk is possible distress caused by completing the tests of memory or other thinking skills and the questionnaires. If you experience distress during the memory testing, please understand that you can stop at any
time and rest until you are ready to continue, or decide not to continue. If you experience distress while completing the questionnaires, you can choose not to answer any questions that you do not want to answer. One of the investigators will be available during these times to meet with any participant, upon request, to discuss any concerns. You can also ask to meet with a member of the research team by calling Dr. Mary Beth Spitznagel at 330.672.2399 (office phone).

For those assigned to the exercise group, exercise may cause muscle soreness. Additionally, exercise could result in heart attack or stroke; this risk for such effects is low, and is further decreased when an individual exercises with their physician’s approval, and in a controlled group setting such as that provided in this study. The research staff will carefully monitor your heart rate to ensure you exercise within a predetermined range. A minimum of two CPR/AED certified individuals and one lifeguard will be present to ensure safety. In addition, exercise will be conducted in the shallow end of the pool. Please inform a research team member if you should wish to stop, experience concern regarding exercise equipment or facilities, or happen to experience any of the following during this study: chest pain, shortness of breath, pallor, fainting, wheezing, leg cramps, light-headedness, confusion, nausea, cold/clammy skin, noticeable change in heart rhythm, severe fatigue, or any other discomfort.

If findings emerge during this research that might affect your willingness to continue to participate, this information will be provided to you so that you can make an informed decision about your participation. For example, if it becomes apparent during the course of the study that you are having significant difficulties with your memory or other thinking skills, we will discuss this with you and may request further evaluation to ensure your safety.

Medical treatment by the University Health Center is provided only to currently registered students. Please be advised that for all other injuries, emergency services will be called for those occurring on the Kent State University campus. You or your medical insurance will be billed for this service. No other medical treatment or financial compensation for injury from participation in this research project is available.

**Criteria for Inclusion/Exclusion:**

**Inclusion:** To be included in this study, you must be between the ages of 20-65, diagnosed with Multiple Sclerosis, have physician approval to participate, and able to communicate in English.

**Exclusion:** You will not be eligible if you have a history of significant neurological disorders other than MS, such as stroke, seizures, or severe head injury. You will not be eligible if you have a history of significant psychological problems, such as schizophrenia or bipolar disorder.
Privacy and Confidentiality: All results will be kept confidential. As soon as possible, your personal identifying information such as your name and date of birth will be removed from your file. We will store all study materials in a locked filing cabinet in a locked room at Kent State University. Your research information may, in certain circumstances, be disclosed to the Institutional Review Board (IRB), which oversees research at Kent State University, or to certain federal agencies. Confidentiality may not be maintained if you indicate that you may do harm to yourself or others.

Compensation: If you take part in this project, you will be compensated $50 for each testing session (total of $100). In addition, if assigned to the Exercise Group, you will be compensated an additional $10 for each day that you attend the exercise group. If you complete all 7 days of exercise, you will receive a $30 completion bonus at the final session. Participants will receive an additional $20 for completing the 12 week telephone follow-up.

Voluntary Participation: Taking part in this research study is entirely up to you. You may choose not to participate or you may discontinue your participation at any time without penalty or loss of benefits to which you are otherwise entitled. You will be informed of any new, relevant information that may affect your health, welfare, or willingness to continue your study participation.

Contact Information: If you have any questions or concerns about this research, you may contact Dr. Mary Beth Spitznagel at 330.672.2399. This project has been approved by the Kent State University Institutional Review Board. If you have any questions about your rights as a research participant or complaints about the research, you may call the IRB at 330.672.2704.

By signing this form I acknowledge that I have read it, understand it, and have had any questions regarding the risks and benefits of this study satisfactorily answered, and I am voluntarily consenting to participate in this study. I have received permission from my physician to participate in this exercise study. If any changes in my health status occur during the course of this study (e.g., new diagnosis, change in medication, etc), I will discuss my continued eligibility with my physician. I realize that by signing this form I do not waive any of my legal rights, and that I can choose to terminate my participation at any time.

_________________________________________ Date: _________________
Participant Signature

_________________________________________ Date: _________________
Witness Signature

________________________________________________________________________ Date: __________

Person obtaining consent

________________________________________________________________________ Date: __________

Investigator

By signing the below, I give permission to be contacted for future studies, and provide my contact information for this purpose. In signing this section, I am only giving permission for the researchers to contact me to inform me of future projects, and am not at this time committing to participate in future studies.

________________________________________________________________________ Date: __________

Participant Signature

Telephone: ___________________________ Email: __________
APPENDIX B

PRE-PARTICIPATION PHONE SCREENING
Appendix B
Pre-Participation Phone Script/Screening Protocol

Study fliers will be located in the lobby of Neurology and Neuroscience Associates (based in Akron, OH), which treats neurologic conditions including MS, and provided to local MS support group locations. The fliers ask interested individuals to contact study personnel. The physician approval form is on the back of the fliers. Prospective participants are responsible for obtaining physician approval on this form.

Prospective participants will be scheduled for a prescreening phone interview. The following phone script will be used:

“Hello, I received your name because you expressed interest in the Multiple Sclerosis study that is taking place at Kent State University. The study will look at the effects on thinking skills of a brief one week water aerobics exercise program developed for individuals with Multiple Sclerosis. Would you be interested in hearing more?”

- If the individual does not express interest, the phone interviewer will thank the individual, and offer contact information if they become interested at a later time.
- If the individual does express interest the conversation would continue as follows:

“Participants will come to the Kent State University Exercise Physiology Lab for two testing days, one at the beginning of the study, and one a week later after the exercise program has been completed. Each testing day will require up to two and a half hours. During the testing session, participants can expect to have thinking skills, blood oxygen levels, body composition, and physical fitness assessed through several simple tests. We will also give you a small monitor to wear home—this will measure your physical activity throughout the following week. All techniques are non-invasive.

Participants will then be randomly assigned to an exercise group or a non-exercise group—that means you will not get to choose if you are in the exercise group or not. The exercise group will participate in a 7 consecutive day water aerobics exercise program that will be about 60 minutes each day, here at Kent State University. Everyone, regardless of whether you are doing the exercise or not, will be asked to complete the two testing days and wear the physical activity monitor.

Are you interested in seeing if you are a candidate for this study?”

- If no, thank the individual for their time
• If yes, (note that they are English speaking) and ask the following:

Have you been diagnosed with MS by a neurologist?
Are you 20-65 years of age?
Do you have physician approval for this study?
Are you pregnant or at risk for becoming pregnant?
Do you have a history of non-MS related neurological disorder or injury such as brain injury or seizure?
Do you have a past or current history of psychiatric illness such as schizophrenia or bipolar disorder?
Do you have past or current history of drug or alcohol abuse?
Do you have a history of learning disorder or developmental disability?
Do you have impaired sensory function that would prevent cognitive testing (for example, being deaf or blind)?

• If individual meets inclusion/exclusion criteria, they are eligible to participate in the study with physician approval. Continue with:

“Would you like to schedule an appointment for the first testing session?”

   - If no, “Thank you for your time.”
   - If yes,
     - schedule the appointment, or develop a timeline to schedule
       - “You will be required to sign a consent form prior to participating”
       - “You must bring the physician approval form that is on the back of our study flier on the date of your first appointment.”
       - “Please wear comfortable clothing and tennis shoes to the first appointment”
       - “If you wear eye glasses, please bring them”

   - If yes, but does not have physician approval yet:
     - “In order to participate in this study you will be required to get physician approval. The approval form is on the back of our flier.”
APPENDIX C
PHYSICIAN CLEARANCE FORM
Appendix C

Physician’s Clearance For Exercise Participation
Kent State University- Dept. of Exercise Physiology

Patient’s name:
Address:
Telephone number:

Dear Doctor-

Your patient, ________________, has expressed an interest in participating in an aquatic aerobics exercise study in individuals with Multiple Sclerosis (KSU IRB approval ____________). The objective of this project is to demonstrate the feasibility and tolerability of a brief water aerobics exercise intervention and determine cognitive benefits of this intervention.

The participant will complete 7 consecutive days of aquatic interval aerobic exercise sessions. Each session include a 10 minute warm up, 40 minutes of low to moderate intensity exercise at 45-55% age-adjusted maximum heart rate broken up into alternating four minutes of exercise followed by one minute of rest, and a 10 minute cool down. The exercise sessions will last 60 minutes. We will examine changes in cognition and fitness parameters after the exercise sessions are completed.

Below is a clearance form to be filled out and signed by you.

Physician’s recommendation (check the appropriate line)
a.________There is no contraindication for participation in this exercise research project.

b.________Because of the following diagnosis, participation in this exercise research program is inadvisable.

Physician’s name: ____________________________________________

Physician Signature: __________________________________________

Date: _______________________________________________________

Address:
Telephone:
APPENDIX D

DATA SHEETS
### Appendix D

#### Data Sheets

**Pre and Post Test Data Sheets**

Data Sheet Body Composition and Cardiovascular Fitness

Subject ____________________________

circle: PreTest Post Test Date ___________________

<table>
<thead>
<tr>
<th></th>
<th>PreTest</th>
<th>Post Test</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: _______ (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender: M / F</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of MS Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height: _______ (ft/in)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight: _______ (lbs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist Circumference _______ (in/cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip Circumference _______ (in/cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist/ Hip Ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Mass Index (BMI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RHR (radial) _______ (bpm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting Blood Pressure _______ (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Arterial Pressure (calculated as diastolic pressure + 1/3 (systolic – diastolic))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tympanic body temperature</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age Adjusted Max Heart Rate</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Direction for Waist and Hip Circumference:**

- **Procedure**
  - The individual is standing, feet together, arms at sides, at the end of expiration.
  - **Waist circumference** is measured at the waist (midpoint between lower margin of the last palpable rib and the iliac crest)
  - **Hip circumference** is measured at the widest portion of the buttocks with the tape parallel to the floor.
  - Two measures are taken and if within 1 cm of each other, the measures are averaged. If the measures are not within 1 cm, the measurements are retaken.
  - **Waist to Hip ratio** is the waist circumference divided by the hip circumference.

- **Scoring**
  - **Waist circumference**: A waist size greater than 35 inches for women and 40 inches for men indicates a greater risk
  - **Waist to hip ratio**: According to the World Health Organization (WHO) Obese is greater than 0.9 for males and 0.85 for females.
Directions for Body Mass Index

- Use the individual’s height and weight to determine the BMI score

<table>
<thead>
<tr>
<th>BMI Classification Chart</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td><strong>Anorexia</strong></td>
</tr>
<tr>
<td><strong>Underweight</strong></td>
</tr>
<tr>
<td><strong>Normal</strong></td>
</tr>
<tr>
<td><strong>Marginally overweight</strong></td>
</tr>
<tr>
<td><strong>Overweight</strong></td>
</tr>
<tr>
<td><strong>Very overweight or obese</strong></td>
</tr>
<tr>
<td><strong>Severely obese</strong></td>
</tr>
<tr>
<td><strong>Morbidly obese</strong></td>
</tr>
<tr>
<td><strong>Super obese</strong></td>
</tr>
</tbody>
</table>
25 Foot Walk Test

Walk Time ___________________________________
Comments ___________________________________ (i.e.: ambulatory device required?)

- Procedure
  - Subject is directed to one end of a clearly marked 25 foot course and is instructed “Please walk as quickly but safely as possible to the end of the 25 foot course”
  - The time is calculated from the initiation of the instruction to start and ends when the subject has reached the 25 foot mark.
  - The task is immediately administered again by having the subject walk back the same distance.
  - Subjects may use assistive devices during this task.
- Scoring
  - The time it takes to walk 25 feet.
    - Trial 1______________________________
    - Trial 2______________________________
    - Average of trial 1+2 ___________________
2 Minute Step Test

# of full steps

- **Procedure**
  - Subject marches in place.
  - A full step consists of raising the knee midway between the patella and iliac crest.
  - Subject steps for 2 minutes

- **Scoring**
  - The number of times the **right** knee reaches the required height
  - Scores less than 65 were associated with lower levels of functional ability
Timed Up and Go Test (TUG)

Average TUG Time _____________________________________________

- Procedure
  - The course is set up with a firm chair with arms (seat height 46 cm) separated by a cone 3 meters apart.
  - The subject begins sitting, back against the chair, arm on the lap, feet just behind the distance marker on the floor.
  - The subject is instructed “on the word ‘go’, stand up, walk comfortably and safely to the cone on the floor, walk around the cone, come back, sit all the way back in your chair.”
  - Timing begins on ‘go’ and stops when the subject has their back against the chair seat.
  - One practice trial and 2 recorded trials are given.

- Scoring
  - The two recorded trial times are averaged.

  Trial 1 time ______________________________
  
  Trial 2 time ______________________________
  
  Average time ____________________________
Rate of Perceived Exertion (RPE)

RPE_________________________

<table>
<thead>
<tr>
<th>Rating</th>
<th>Perceived Exertion</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>No exertion</td>
</tr>
<tr>
<td>7</td>
<td>Extremely light</td>
</tr>
<tr>
<td>8</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Very light</td>
</tr>
<tr>
<td>10</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Light</td>
</tr>
<tr>
<td>12</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Somewhat hard</td>
</tr>
<tr>
<td>14</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Hard</td>
</tr>
<tr>
<td>16</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Very hard</td>
</tr>
<tr>
<td>18</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Extremely hard</td>
</tr>
<tr>
<td>20</td>
<td>Maximal exertion</td>
</tr>
</tbody>
</table>

Table 1. The Borg Rating of Perceived Exertion Scale

- **Procedure**
  - The subject is asked to circle the number that describes where they feel their intensity level is.

- **Scoring**
  - Subjective assessment, but does correlate to maximal heart rate
NIRS (Near Infrared Spectroscopy)

<table>
<thead>
<tr>
<th>Resting Oxyhemoglobin</th>
<th>Resting Deoxyhemoglobin</th>
<th>Resting Total Hemoglobin</th>
<th>Cognitive oxyhemoglobin</th>
<th>Cognitive deoxyhemoglobin</th>
<th>Cognitive total hemoglobin</th>
</tr>
</thead>
</table>

% change resting – cognitive oxyhemoglobin: ______________________________

% change resting – cognitive de-oxyhemoglobin: _____________________________

% change resting – cognitive total hemoglobin: _____________________________

- **Procedure**
  - Have subject rest for 2 minutes sitting (or supine)?
  - Placement of sensor 2 cm away from midline, 1 cm above supraorbital ridge, eyes closed.
  - Measure baseline for 2 minutes
  - Continue measurement while administering N-back test

- **Scoring**
  - Compare through % change of average resting and cognitive values for Hemoglobin, deoxyhemoglobin, and total hemoglobin
APPENDIX E

HEART RATE AND RPE
Appendix E

Heart Rate and RPE

Figure 20, Exercise group average Rate of Perceived Exertion during pre-exercise, warm-up, and interval 6 of the exercise intervention.

Figure 21, Exercise group average heart rate during pre-exercise, warm-up, and interval 6 of the exercise intervention.
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