Brain-based evidence for aerobic exercise as a treatment for Multiple Sclerosis

by

Chantel Dana Mayo
B.Sc., University of Winnipeg, 2013
M.Sc., University of Victoria, 2016

A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of

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In the Department of Psychology

We acknowledge with respect the Lekwungen peoples on whose traditional territory the university stands and the Songhees, Esquimalt and WSÁNEĆ peoples whose historical relationships with the land continue to this day.

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Abstract

Multiple Sclerosis (MS) is a chronic neurological condition typically diagnosed in early adulthood that often requires lifelong treatment for symptom management. Despite pharmacological treatment, many individuals with MS continue to experience symptoms. Exercise may hold promise for MS treatment, but changes in brain structure following exercise have not been thoroughly investigated, and important cognitive and psychosocial symptoms are less frequently included as primary outcome measures. This dissertation is comprised of three manuscripts that investigate the relationships between exercise, white matter microstructure, and cognitive and psychosocial symptoms in MS. *Study One:* The first study used a mail-out questionnaire to investigate the relationship between physical activity and common MS symptoms, including fatigue, depressed mood, and perceived cognitive impairment. Results indicated that individuals with MS who reported more strenuous and/or frequent physical activity reported less fatigue, less depression, and fewer perceived memory problems. *Study Two:* The second study used a type of magnetic resonance imaging known as diffusion tensor imaging (DTI), along with neuropsychological measures and questionnaires to investigate whether reported physical activity, neuropsychological performance, and common self-reported MS symptoms of fatigue and depressed mood were related to brain structure in relapsing-remitting MS (RRMS). There was no evidence of a relationship between white matter microstructure and level of physical activity for individuals with RRMS, nor was there evidence for a relationship between white matter

microstructure and MS symptoms related to cognition, fatigue, and mood. *Study Three:* The third study used pre- and post- intervention DTI, neuropsychological testing and self-report questionnaires to investigate whether a 12-week exercise intervention improved white matter microstructure, cognition, or symptoms of fatigue and depressed mood in RRMS. Results indicated that following a 12-week exercise intervention, individuals with RRMS performed better on measures of information processing speed, reported fewer prospective memory problems, and reported fewer problems with fatigue. There were no increases or decreases in white matter microstructure. Together, these studies suggest that exercise may be helpful in the management of some cognitive and psychosocial MS symptoms.

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Additionally, I had the opportunity to consult with individuals with lived experience with MS who were able to provide critical insight into the nature of their MS. Their personal accounts and curiosities truly set the foundation for this work. As a strong advocate for patient-oriented research, it was important to me that our research sought to answer relevant questions and include outcome measures that are meaningful to those affected by MS. Thank you to those with lived experiences with MS who have shared their stories, provided feedback on our study design, and/or participated in our research.

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Dedication

This work is for you, M.

Introduction

Multiple Sclerosis (MS) is a heterogeneous chronic disease affecting the central nervous system (CNS), leading to the accumulation of physical disability and a variety of sensory, motor, cognitive and psychosocial symptoms (Compston & Coles, 2008; Lassman, 2018). Over 2.2 million individuals are diagnosed with MS worldwide, and Canada is among the countries with the highest prevalence (Wallin et al., 2019). For example, estimated rates of MS range from 180/100,000 in British Columbia (Kingwell et al., 2015), to 227/100,000 in Manitoba (Marrie, Yu, Blanchard, Leung, & Elliott, 2010), to 267/100,000 in Nova Scotia (Marrie et al., 2013).

MS Pathology

First described by Charcot in 1880, MS is an inflammatory disease that affects myelin in the brain and spinal cord of the CNS. Focal areas of myelin loss known as lesions or plaques are the hallmark diagnostic features of MS (Popescu, Pirko, & Lucchinetti, 2013). See Figure A1 in Appendix A for sample images of MS lesions. Historically, CNS lesions within white matter have been the focus of MS pathology investigations, however more recent evidence suggests lesions may present in gray matter as well (Popescu, et al., 2013; Lassman, 2018).

The evolution of lesions is variable across the disease course, but new active lesions occur most frequently early on in the disease course (Lassman et al., 2018). Although lesions can be found throughout the central nervous system, they are most commonly observed in the periventricular, cortical/juxtacortical, infratentorial

(cerebellar) and spinal cord regions (Popescu et al., 2013; Thompson et al., 2017). Several complex pathological processes are thought to contribute to the formation of MS lesions, including inflammation, demyelination, astrogliosis, oligodendrocyte injury, neurodegeneration, and axonal loss (Popescu et al., 2013).

Risk Factors for MS

The ultimate cause of MS pathology is unknown, but the risk of developing the disease is thought to involve a combination of genetic and environmental risk factors (Compston & Coles, 2008; Belbasis, Bellou, Evangelou, Ioannidis, Tzoulaki, 2015). To date, the largest known genetic risk factor is the human leukocyte antigen *DRB1*1501*, an allele that increases risk of MS by up to three times (Parnell & Booth, 2017). Sex is also a significant genetic risk factor, with females two to three times more likely to have MS than males (Howard, Trevick, & Younger, 2016).

Numerous environmental risk factors have also been explored (see Amato et al., 2016 for a review). One review of systematic reviews and meta-analyses suggested that exposure to Epstein-Barr virus, smoking, and infectious mononucleosis were the strongest, most consistent environmental risk factors for MS (Belbasis et al., 2015). Other established environmental risk factors include low vitamin D and lack of sun exposure (Munger et al., 2006; Olsson & Alfredsson, 2016)

Diagnosis of MS

There is no single pathognomonic sign of Multiple Sclerosis (MS). The 2017 McDonald criteria for the diagnosis of MS combines clinical history, magnetic resonance imaging (MRI), and laboratory evidence in order to characterize clinical

attacks and the number of CNS lesions (Thompson et al., 2017). On MRI of the brain and spinal cord, there must be evidence of dissemination in time (i.e., development of new lesions over time) and dissemination in space (i.e., development of lesions in distinct anatomical locations) to support a diagnosis. A full summary of the McDonald criteria used in the diagnosis of MS is outlined in Table B1 in Appendix B.

MS Clinical Course

Given the heterogeneity in clinical presentations, standardized MS clinical course descriptors have been developed and refined, most recently by the International Advisory Committee on Clinical Trials of MS (Lublin & Reingold, 1996; Lublin et al., 2014), to aid in communication among clinicians and inform prognosis of disease course as well as treatment decision-making. According to the committee's guidelines, the MS clinical course should be specified at the time of diagnosis and periodically re-evaluated across time as new information becomes available.

Clinically Isolated Syndrome

Approximately 80% of individuals first present with an acute episode indicative of Clinically Isolated Syndrome (CIS; Compston & Coles, 2008). A diagnosis of CIS is often given following the first presentation of neurological symptoms suggestive of an inflammatory CNS demyelination (Lublin et al., 2014). However, individuals with CIS have not yet demonstrated evidence of dissemination in time, which is necessary for the diagnosis of MS. Individuals with CIS may or may not go on to develop MS.

Relapsing-Remitting MS

Relapsing-Remitting MS (RRMS) is the most common disease course occurring in up to 85% of individuals. RRMS is characterized by worsening of neurologic functioning (relapses) and accumulation of MS-related disability, followed by periods of partial or complete recovery (remissions) with no disease progression (Lublin et al., 2014).

Secondary Progressive MS

Secondary Progressive MS (SPMS) is characterized by a gradual, progressive worsening of neurological functioning and accumulation of MS-related disability, after an initially relapsing-remitting disease course (Lublin et al., 2014). Up to 80% of individuals initially diagnosed with RRMS will eventually transition to SPMS (Chiaravalloti & DeLuca, 2008). However, the transition from RRMS to SPMS is gradual, and there are no clear criteria for determining the exact transition point (Lublin et al., 2014).

Primary Progressive MS

Primary Progressive MS (PPMS) is characterized by a progressive worsening of neurological functioning and accumulation of MS-related disability from the beginning of the disease course (Lublin et al., 2014). Approximately 15% of individuals diagnosed with MS have PPMS (Hauser et al., 2013).

Symptoms of MS

Most individuals with MS experience their first symptoms in early to mid adulthood (mean age = 32.0 years, Gilmour, Ramage-Morin & Wong, 2018; mean age

= 31.4 years, Kister et al., 2013). Given that MS lesions can be distributed throughout the CNS, individuals with MS can experience numerous, diverse symptoms. Traditionally, sensory and motor symptoms were thought to be the primary symptoms of MS, but there has since been a greater recognition of the complex cognitive and psychosocial symptoms that may also present.

Sensory and Motor

Up to 85% of individuals with MS report sensory changes (Kister et al., 2013). Sensory symptoms can include numbness or tingling sensations in the limbs. Additional visual changes such as optic neuritis, diplopia, and acuity changes may also occur (Bobholz & Gremley, 2011). Common motor symptoms include weakness, problems with gait, problems with balance, and discoordination, dysphagia, and dysarthria (Bobholz & Gremley, 2011; MS Society of Canada, 2017). Other symptoms, including sexual dysfunction and bladder dysfunction are also common in MS.

Cognitive

Up to 70% of individuals with MS experience impairments across multiple cognitive domains such as information processing, divided and sustained attention, memory recall, and executive function tasks of shifting, inhibition, and fluency (Benedict & Zivadinov, 2011; Chiaravalloti & DeLuca, 2008; Planche, Gibelin, Cregut, Pereira, & Clavelou, 2016). Simple attention and basic language skills (e.g., word naming, comprehension) often remain intact, as does general intellectual function (Chiaravallotti & DeLuca, 2008; Rao, 2004; Rocca et al., 2015). Cognitive

impairments are often associated with poor psychosocial functioning (Rocca et al., 2015). Individuals with MS-related cognitive impairments can experience reduction in activities of daily living, employment, hobbies, and social activities (Benedict et al., 2017; Rao, 2004).

Individuals with progressive forms of MS (PPMS, SPMS) tend to experience greater cognitive impairment than those with RRMS (Hujibregts et al., 2004; Ruet et al., 2013; Planche et al., 2016). A recent study comparing neuropsychological profiles among individuals with RRMS, SPMS, and PPMS found that individuals with PPMS and SPMS performed worse on neuropsychological tests of processing speed, memory recall, executive function, visuospatial construction, working memory, verbal fluency compared to individuals with RRMS, with a notable exception for word naming, where performance was similar. The only significant difference in performance among individuals with progressive forms of MS was that individuals with SPMS tended to have poorer performance on visuospatial construction compared to PPMS (Planche et al., 2016).

Fatigue

Fatigue is among the most commonly reported symptoms of MS (Asano & Finlayson, 2014; Bakshi 2003). Approximately 50% to 80% of individuals with MS experience fatigue (Wood et al., 2012; Zajicek et al., 2010) and 40%-75% report that fatigue is their most disabling symptom (Bakshi 2003; Fisk, Ponteract, Ritvo, Archibald, & Murray, 1994; Krupp et al., 1988). Fatigue often limits psychosocial functioning (e.g., ability to maintain full time employment; Jongen et al., 2014) and quality of life (Garg, Bush, & Gappmaier, 2016).

Mood

Depressed mood is another common symptom of MS. Recent estimates from Statistics Canada suggest that individuals with MS were more than three times more likely to have a mood disorder than the general population (Koch et al., 2015; Gilmour et al., 2018). Up to 50% of individuals diagnosed with MS have experienced depression at some point in their lifetime (Feinstein et al., 2014; Koch et al., 2015). Reasons for the higher rates of depression in MS are still being explored, but are thought to be both psychosocial (e.g., reaction to a chronic disease and disability) and physiological (e.g., underlying brain pathology, including inflammation) in nature (Boeschoten et al., 2017; Koch et al., 2015; Rossi et al., 2017; Siegert & Abernethy, 2005).

Treatment of MS

There is no known cure for MS. Many individuals with MS rely on pharmaceuticals for long-term medical management. For individuals with RRMS, interferon beta and glatiramer acetate are the first-line disease modifying treatments. Fingolimod and natalizumab are second line treatments for individuals who are not able to tolerate first-line treatments or have much more active RRMS (Freedman et al., 2013). Pharmaceutical treatments for progressive MS are much more limited than RRMS, but recently, ocrelizumab has been used as a first-line treatment for PPMS (Montalban et al., 2016).

Unfortunately, pharmaceutical treatments are expensive (e.g., estimated to cost over $50,000 USD per year; Hartung et al., 2015), and are often accompanied by side effects. For example, interferon beta is estimated to reduce the rate of relapse

in approximately 30-34% of individuals with MS, but up to 75% experience side effects such as fever, headache, and pain (Torkildsen et al., 2016).

In addition to disease modifying treatments, concurrent pharmaceuticals may also be prescribed for symptom management, such as muscle relaxant for motor symptoms, antidepressants for mood, CNS stimulants for fatigue (MS Society of Canada, 2018).

Exercise with MS

Exercise has emerged as a promising complementary, or even alternative, option to pharmaceuticals. It is low-cost, accessible, and non-invasive (Heine et al., 2015). Historically, individuals with MS were advised to avoid strenuous exercise due to the concerns of overheating and acute symptom exacerbations (Giesser, 2015; Petajan & White, 1999). Petajan and colleagues (1996; 1999) first challenged this notion by demonstrating that individuals with MS were in fact able to tolerate exercise, and that it seemed to have a positive impact on factors relevant to quality of life. It is now increasingly accepted that it is safe for individuals with MS to engage in exercise. Findings from a recent systematic review on the safety of exercise interventions suggested that individuals with MS were no more likely than healthy individuals to experience adverse health events due to exercise (Pilutti, Platta, Motl, & Latimer-Cheung, 2014).

Generally, exercise is thought to promote anti-inflammatory effects through various physiological mechanisms (for a full review, see Guo, Lozinski & Wee Yong, 2020). Cytokines, the immunomodulatory signalling molecules produced by immune cells, are thought to play a key role (Svensson et al., 2015). While some

cytokines are pro-inflammatory, promoting inflammatory processes, others are anti-inflammatory, ultimately reducing inflammation. There is evidence that physical activity can lead to decreased levels of pro-inflammatory cytokines and increased levels of anti-inflammatory cytokines, ultimately contributing to decreased inflammation overall.

Furthermore, exercise is also thought to promote neurotrophic factors (e.g., brain-derived neurotrophic factor; Svensson et al., 2015; White and Castellano, 2008). Secreted naturally from cells, neurotrophic factors act on the neuron receptors to promote neuronal survival; lack of neurotrophic factors are thought to contribute to neurodegeneration (Svensson et al., 2015). Thus, exercise may contribute to increased neurotrophic factors that support neuron growth and survival, ultimately helping to protect neurons from neurodegeneration.

Given that MS is a chronic inflammatory, demyelinating, and neurodegenerative disease, exercise holds promise for management of MS symptoms from a physiological perspective (Lassman 2018; Perez-Cerda, Sanchez-Gomez, & Matute, 2016; Svensson et al., 2015).

To date, the majority of MS and exercise research has involved animal models of neurodegeneration, including experimental MS mouse models (e.g., experimental autoimmune encephalomyelitis; Klaren, Motl, Woods, & Miller, 2014). However, there is preliminary evidence that exercise is neuroprotective in humans with MS as well. For example, a single case study of an individual with RRMS demonstrated increases in hippocampal volume, hippocampal resting state functional connectivity, and memory performance, following a three-month aerobic

exercise intervention performed for 30 minutes three times per week (Leavitt et al., 2014).

Magnetic Resonance Imaging in MS

Despite a limited number of case studies, changes to the brain following exercise have not yet been thoroughly investigated in individuals with MS. One means to investigate this further is through the use of magnetic resonance imaging (MRI), a non-invasive, safely repeatable technique used to visualize brain structure *in vivo*. Indeed, structural MRI is already routinely used in the assessment and diagnosis of MS in clinical contexts (see Figure B1 in Appendix B), as well as in monitoring subsequent disease progression (Filippi et al., 2011; Thompson et al., 2017). The International Panel on the Diagnosis of Multiple Sclerosis recommends that all individuals being considered for the diagnosis of MS receive a brain MRI, where possible (Thompson et al., 2017). Clinically, T2- or gadolinium-enhanced T1-weighted MR sequences are used to visualize MS lesions, which appear hyperintense (i.e., white) relative to normal appearing brain tissue (Rovira, Auger, Alonso, 2013).

One type of MRI scan that may be particularly useful for investigating brain changes in MS following exercise is diffusion tensor imaging (DTI). In DTI, the movement of water in the brain can be used to calculate indices of white matter integrity (Alexander et al., 2007). Because DTI gives information about water diffusion within brain tissues, microstructural changes in white matter may be observed earlier than on conventional MRI (Commowick, Fillard, Clatz, & Warfield, 2008). Thus, DTI's sensitivity to microstructural changes in white matter make it an

ideal tool to investigate the effects of exercise on brain structure in individuals with MS over time.

There are four commonly reported DTI metrics used to describe the microstructural characteristics of white matter: 1) Fractional anisotropy (FA), a measure of the degree of directionality of the water diffusion; 2) mean diffusivity (MD), a measure of the water diffusion rate; 3) axial diffusivity (AD), a measure of the rate of water diffusion parallel to a fibre tract; and 4) radial diffusivity, a measure of the rate of water diffusion perpendicular to a fibre tract (Alexander et al., 2007; Jellison et al., 2004; Sbardella et al., 2013).

When pathological processes affect the tissues in the brain, as is the case in MS, alterations in DTI metrics can be observed. Decreased FA is indicative of progressive loss of barriers that restrict water diffusion in healthy white matter. Several factors may influence FA value including myelination level and axon density (Bosch et al., 2012). As such, FA is thought to give an overall *in vivo* indication of microstructural integrity in white matter tissue (Pierpaoli et al., 1996; Gold, 2012; Stebbins & Murphy, 2009). Relatedly, increased MD is indicative of greater rates of water diffusion in the brain; this may occur as a result of tissue breakdown as is the case in brain trauma or disease (Gold, 2012). More specifically, AD is thought to reflect axonal integrity, with decreases in AD potentially reflecting axonal loss (Fox 2008; Gold, 2012; Sbardella et al., 2013; Song et al., 2002). RD is thought to reflect myelin integrity, with increases in RD indicating loss of myelin (Fox 2008; Gold, 2012; Song et al., 2002). Please see Appendix C for more information about the physics of DTI.

Overview of Studies

This manuscript-based dissertation is comprised of three studies, described below. Despite the greater recognition of the cognitive and psychosocial symptoms that accompany MS, they are not often the primary outcome measures in most MS exercise studies. Thus, rather than focusing on traditional physical outcome measures, all three studies comprising this dissertation included cognition and psychosocial symptoms as key outcome measures. Furthermore, the lack of studies that use MRI to examine the effect of exercise in MS is a critical gap in the literature (Giesser, 2015; Motl & Sandroff, 2015). Additional research with MRI outcomes is needed to determine whether exercise may be related to positive alterations in brain structure, which could provide further evidence that exercise is neuroprotective for MS. Thus, two studies have included DTI metrics.

It is also important to note that the goals of each of these studies, while rooted in the current literature, were also guided by individuals with lived experience with MS. Throughout this dissertation, we employed a strong patient-oriented approach, seeking to answer questions and include outcome measures that hold meaning to individuals affected by MS through direct consultation with these community members.

Study 1: The Relationship Between Physical Activity, Fatigue, Mood, and Perceived Cognitive Impairment in Adults with Multiple Sclerosis

The goal of the first study was to investigate the relationship between physical activity and common MS symptoms, including fatigue, depressed mood, and perceived cognitive impairment. Data were collected via mail-out questionnaires.

Relationships were examined at the overall group level (those diagnosed with MS, regardless of subtype) as well as separately at the subgroup level (diagnosed with RRMS; diagnosed with progressive MS).

Study 2: Are Physical Activity, Neuropsychological Performance, and Self-Reported Symptoms Related to Brain Structure in Individuals with Relapsing-Remitting Multiple Sclerosis?

The goal of the second study was to investigate whether reported level of physical activity, neuropsychological performance, and common symptoms of fatigue and depressed mood were related to brain structure. All participants were diagnosed with RRMS. Non-imaging data were collected using neuropsychological testing and self-report measures. Imaging data were collected on a 3T MRI scanner. Brain structure was assessed using diffusion tensor imaging metrics.

Study 3: A Pilot Study of the Impact of an Exercise Intervention on Brain Structure, Cognition, and Psychosocial Symptoms in Individuals with Relapsing-Remitting Multiple Sclerosis

The goal of the third study was to investigate whether a 12-week exercise intervention (speeded walking) would improve white matter integrity in the brain, cognition, and symptoms of fatigue and depressed mood. All participants were diagnosed with RRMS. Data were collected pre- and post- intervention using neuropsychological testing, self-report measures, and diffusion tensor imaging.

Study One: The Relationship Between Physical activity, Fatigue, Mood, and Perceived Cognitive Impairment in Adults with Multiple Sclerosis

This chapter includes published work: **Mayo, C.D.,** Miksche, K., Atwell-Pope, K., & Gawryluk, J. (2019). The relationship between physical activity, fatigue, mood, and perceived cognitive impairment in adults with multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology,* 41, 715-722, doi: 10.1080/13803395.2019.1614535

Note: This is an Accepted Manuscript of an article published by Taylor & Francis in Journal of Clinical and Experimental Neuropsychology on 16 May 2019 available at http://www.tandfonline.com/10.1080/13803395.2019.1614535

Abstract

Introduction: Multiple Sclerosis (MS) is a chronic neurological disease that is typically diagnosed in young adulthood. Most individuals require costly treatment for the majority of their lives to treat a constellation of motor and sensory symptoms, as well as fatigue, depression, and cognitive problems. Many continue to have debilitating MS symptoms and side effects with pharmacological treatment. As a result, there is a crucial need for low cost behavioural treatments that are effective in further reducing MS symptoms. Physical activity has shown promise in managing other neurological disorders and it has been hypothesized that physical activity may slow the neurodegenerative progression of MS. The aim of the current study was to investigate the relationship between physical activity and commonly reported MS symptoms, including fatigue, depression, and perceived cognitive impairment. **Method**: 86 individuals with MS responded to a mail-out questionnaire. Physical activity, fatigue, mood, and perceived cognitive impairment were assessed using the following measures: Godin Leisure-Time Exercise Questionnaire (GLTEQ), Modified Fatigue Impact Scale (MFIS), Patient Health Questionnaire (PHQ-9), and Perceived Deficit Questionnaire (PDQ). Descriptive and correlational statistics were calculated to investigate the relationship between scores on the GLTEQ and scores on the MFIS, PHQ-9, and PDQ for individuals with MS, individuals with relapsing-remitting MS (RRMS) only, and progressive MS only. **Results**: Overall, there was a significant negative relationship between physical activity (GLTEQ) and fatigue (MFIS; $r = -.34$, $p = .002$) and depression (PHQ-9; $r = -.23$, $p = .034$) in individuals with MS. There was not a significant relationship between physical activity and overall perceived

cognitive dysfunction (PDQ; r = -.19, p = .08), but when the PDQ subscales were examined, there was a significant relationship with perceived retrospective (r= 0.24, p = .03) and prospective memory abilities (r= -.22, p=.04). When the RRMS and progressive subtypes were examined separately, we observed a similar pattern of results for the RRMS group, but the progressive MS group did not reach significance. **Conclusion**: Overall, individuals with MS who reported more strenuous and/or frequent physical activity, reported fewer problems with fatigue, depression, and perceived memory abilities.

Introduction

Globally, 2.5 million individuals experience Multiple Sclerosis (MS), a chronic inflammatory disease characterized by demyelination and degeneration of axons in the central nervous system (Lassman, 2018; Multiple Sclerosis International Federation, 2013). Given that the lesions associated with MS can be distributed throughout the central nervous system, individuals with MS may experience changes in sensory, motor, and cognitive functioning (Compston & Coles, 2008). Up to 70% of individuals with MS experience impairments in multiple cognitive domains such as information processing, episodic memory recall, and executive function (Benedict & Zivadinov, 2011; Chiaravalloti & DeLuca, 2008; Planche, Gibelin, Cregut, Pereira, & Clavelou, 2016). Furthermore, individuals with MS have noted fatigue and dysregulated mood as major issues impacting quality of life (Chiaravalloti & DeLuca, 2008; Benedict & Zivadinov, 2011; Planche, Gibelin, Cregut, Pereira, & Clavelou, 2016); up to 50% of individuals diagnosed with MS have experienced depression (Feinstein et al., 2014) and 50% to 80% of individuals with MS experience fatigue (Wood et al., 2012; Zajicek et al., 2010).

Currently, there is no cure for MS. Most individuals with MS experience their first symptoms in young adulthood (mean age = 31.4; Kister et al., 2013) and rely on pharmaceuticals for long-term medical management, which costs over $50,000 USD annually (Hartung et al., 2015). Interferon beta, a first line pharmaceutical treatment is estimated to reduce the rate of relapse in approximately 30-34% of individuals with MS, but up to 75% of individuals experience side effects (e.g., fever,

headache, and pain) following injections (Torkildsen et al., 2016).

As an alternative to medical management alone, exercise interventions have shown promise in managing other types of neurological disorders including stroke, dementia and Parkinson's disease (Svensson, Lexell, & Deierborg, 2015; Jang et al., 2017). Despite the evidence supporting neuroprotective effects of exercise, patients with MS have traditionally been advised to avoid strenuous physical activity, due to the notion that overheating during exercise could lead to acute symptom exacerbations, especially fatigue (Giesser, 2015; Petajan & White, 1999). However, an early study by Petajan and colleagues (1999) challenged this belief by demonstrating that individuals with MS were not only able to tolerate exercise, but that exercise may actually have a positive impact on factors relating to quality of life. Since this time, it has been increasingly accepted that exercise is safe, and even beneficial, for individuals with MS (Dalgas, Ingemann-Hansen, & Stenager, 2009). A recent systematic review on the safety of exercise interventions indicated that individuals with MS who participated in exercise training were no more likely to experience an adverse health event than healthy individuals (Pilutti et al., 2014).

To date, several reviews and meta-analyses have looked at the impact of exercise interventions for individuals with MS. These studies have provided early evidence that exercise interventions have modest effects on improving MS symptoms (Rietberg, Brooks, Uitdehaag, & Kwakkel, 2005; see also Sa, 2014; Snook & Motl, 2009) and have suggested that exercise may be neuroprotective in individuals with MS (Sa, 2014). However, the major outcomes of these studies have

largely been confined to physical measures (e.g., walking, strength, mobility). The purpose of the current study was to investigate the relationship between physical activity and other prevalent MS symptoms, including fatigue, depression, and perceived cognitive impairment. It was hypothesized that individuals who participated in more frequent and strenuous exercise would report fewer symptoms of fatigue, depression and cognitive impairment.

Methods

Participants

All participants were enrolled in the local health authority's (Island Health) permission to contact program. This program allows researchers to connect with patient populations (e.g., individuals with physician-confirmed diagnoses of MS) to facilitate new research opportunities. During routine health appointments at Island Health clinics, limited personal health information (such as diagnosis and contact information) is collected from patients who are willing to be contacted for future research opportunities. Their information is compiled into a database and accessed when relevant study opportunities arise. Individuals were eligible to participate in the current study if they were over the age of 18, proficient in English, and diagnosed with MS. In total, 92 individuals participated in the current study (See Figure 1.1 for the recruitment flowchart).

The current study was approved by the harmonized human research ethics Board at the University of Victoria and Vancouver Island Health Authority in British Columbia, Canada.

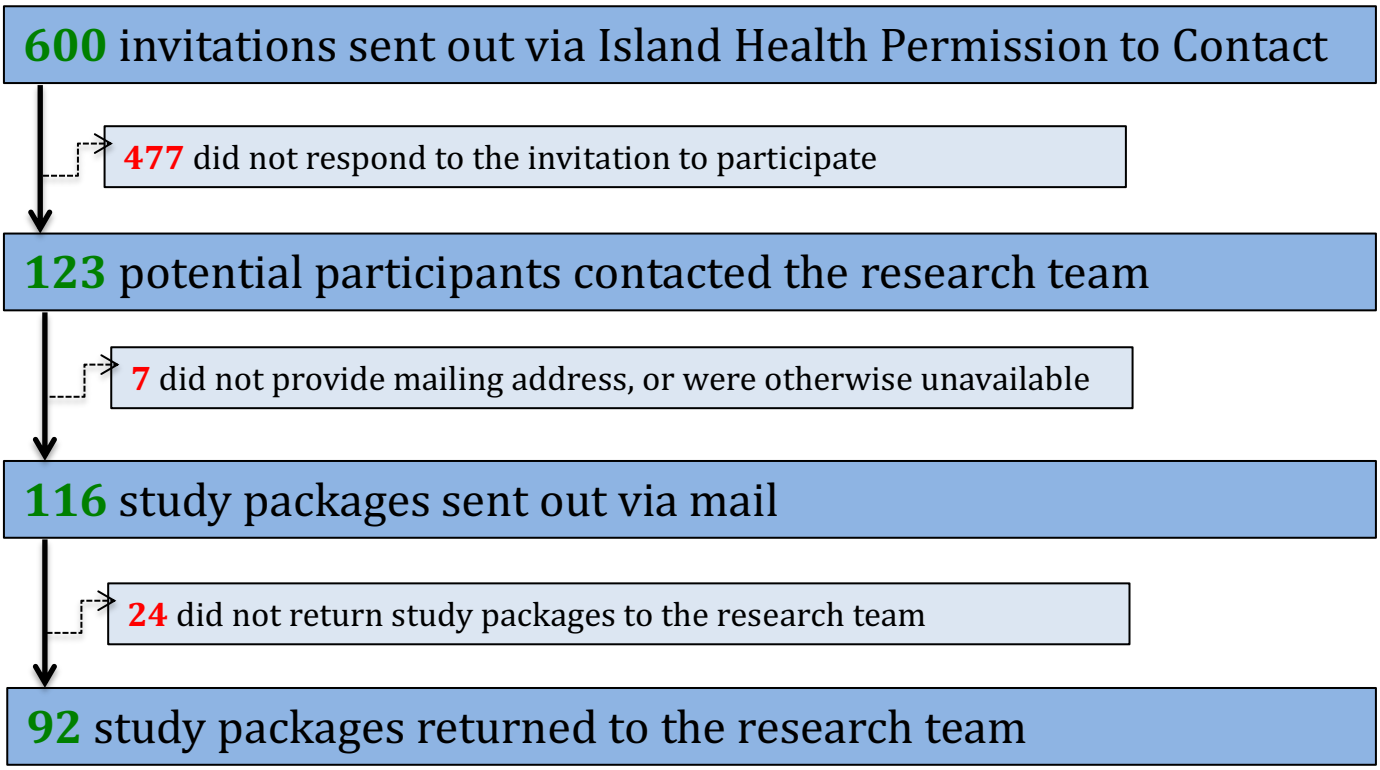

Figure 1.1. Summary of recruitment process

Questionnaires

Physical activity, fatigue, mood, and perceived cognitive impairment were assessed using self-report questionnaires with good psychometric properties (see Appendix D). The self-report questionnaires were chosen according to the following criteria: a) the survey was developed for and/or had been previously used and validated with the MS population; (b) public administration was permissible and thus it was not copyrighted; (c) the questionnaire could be self-administered without a clinician present.

Physical activity. Physical activity was assessed using the Godin Leisure-Time Exercise Questionnaire (GLTEQ; Godin & Sheppard, 1985; Godin, 2011). The GLTEQ is a self-report questionnaire that measures the frequency of physical activity lasting longer than 15 minutes during the past week. Individuals are asked to indicate the frequency of strenuous, moderate, and mild physical activity. The weekly frequency of strenuous (e.g., running), moderate (e.g., fast walking), and mild (e.g., yoga) physical activity is multiplied by 9, 5, and 3, respectively, and then summed to yield a total score. Higher scores are indicative of more frequent and strenuous exercise. The GLTEQ has previously been validated for use with MS populations (e.g., Gosney, Scott, Snook, & Motl, 2007).

Fatigue. The impact of fatigue was assessed using the Modified Fatigue Impact Scale (MFIS), of the MS Quality of Life Inventory (Fisk et al., 1994; Ritvo et al., 1997). The MFIS is a 21 item self-report questionnaire that assesses physical (9 items), cognitive (10 items) and psychosocial (3 items) aspects of fatigue in the past four weeks. Individuals are asked to rate their experience with fatigue on a Likert-scale from 0 (never) to 4 (almost always). The three subtests are summed to yield a total fatigue score. Higher scores (maximum 84) are indicative of a greater impact of fatigue on daily activities.

Mood. Mood was assessed using the Patient Health Questionnaire (PHQ-9; Kroenke, Spitzer, & Williams, 2011). The PHQ-9 is a 9 item self-report questionnaire of depressive symptomatology in the past two weeks. Individuals are asked to rate their mood on a Likert-scale from 0 (not at all) to 3 (nearly every day). Higher scores (maximum 27) are indicative of higher levels of depression. Specifically,

scores between 5 and 9 indicate above average levels of depressive-symptomatology, and scores 10 or above indicate probable major depression. The PHQ-9 has been validated in MS populations (e.g., Patten et al., 2015).

Perceived cognitive impairment. Perceived cognitive impairment (attention/concentration, retrospective memory, prospective memory, and planning/organization) was assessed using the Perceived Deficit Questionnaire (PDQ) of the MS quality-of-life inventory (Ritvo et al., 1997). The PDQ is a 20 item self-report questionnaire of perceived cognitive impairment in the past 4 weeks. Individuals are asked to rate the frequency of cognitive challenges on a Likert-scale from 0 (never) to 4 (almost always). Higher scores (maximum 80) are indicative of greater perceived cognitive deficits.

Statistical Analyses

Descriptive and correlational statistical analyses were performed with R Studio (version 3.1.2, RStudio Team, 2015). Data was initially tested for normality. To test for outliers, a frequency histogram was generated and visually inspected. The assumptions of normality were then tested through visual inspection of frequency histograms, and Shapiro-Wilk normality tests (Royston, 1982a; 1982b; 1995), and Q-Q plots of sample quantiles plotted against theoretical quantiles for each of the variables. Post Hoc analyses of the overall group as well as the progressive MS subgroups were conducted using G*Power (version 3.1.9.2; Faul, Erdfelder, Lang, & Buchner, 2007) to determine achieved power.

Descriptive statistics were calculated for each questionnaire. Spearman correlation coefficients were calculated to investigate the relationship between

scores on the GLTEQ and scores on the (a) MFIS total and subscales; (b) PHQ-9; and (c) PDQ total and subscales. In addition, partial correlation coefficients were calculated to investigate the relationship between scores on the GLTEQ and scores on the (a) MFIS total and subscales; (b) PHQ-9; and (c) PDQ total and subscales, controlling for age. All individuals with MS, regardless of subtype, were combined into one group for the overall analysis. Follow-up separate group analyses were also completed for individuals with relapsing-remitting MS (RRMS) and progressive subtypes of MS (primary progressive MS; secondary progressive MS (PPMS; SPMS)). All correlational statistical analyses were evaluated at $\alpha = 0.05$ (two-sided).

Results

Participant Characteristics

Data were returned for 92 individuals with MS (response rate = 79.3%). Five individuals were not included in the analysis because they did not meet eligibility criteria (3) or did not return demographic information (2). Furthermore, one additional individual's scores were identified as an outlier and removed from the analysis. There were a total of 86 individuals with MS included in the overall analysis, including 58 individuals with RRMS and 24 with progressive subtypes of MS. Please see Table 1.1 for participant demographics.

Table 1.1. *Participant Demographics.*

Total Participants	Mean Age (Years)	Mean Education (Years)	Females	Self-Reported MS Subtype			
				RRMS	SPMS	PPMS	Unknown
86	56.45 ± 12.25	15.27 ± 3.17	68	58	17	7	4

RRMS=relapsing remitting MS, SPMS = secondary progressive MS, PPMS= primary progressive MS

Normality Testing

The Shapiro-Wilk normality tests indicated that the exercise (GLTEQ) scores, $W=0.933$, $p < 0.001$, the mood scores (PHQ-9) $W=0.906$, $p <0.001$, and the perceived cognitive impairment (PDQ) scores, $W =0.970$, $p = .043$ were significantly non-normal. The fatigue scores, $W=0.980$, $p = .218$, were significantly normal.

Power Analysis

Using a two-tailed correlational test to detect a medium (or larger) effect size ($\rho = 0.3$), while also retaining an acceptable false positive rate ($\alpha = 0.05$), the power was 0.822 for our overall sample size of 86 participants, and 0.314 for the progressive MS subgroup.

Questionnaire Characteristics

Descriptive statistics for the self-report questionnaires, GLTEQ, MFIS, PHQ-9, and PDQ are reported in Table 1.2.

Table 1.2. *Descriptive Statistics for the Self-Report Questionnaires: Godin Leisure-Time Exercise Questionnaire (GLTEQ), Modified Fatigue Impact Scale (MFIS), Patient Health Questionnaire (PHQ-9) and Perceived Deficits Questionnaire (PDQ).*

Questionnaire	Mean score	Median score	Standard deviation	Observed Range	Possible Range
GLTEQ	33.94	30	25.87	0-101	≥0
MFIS$_{Total}$*	38.28	41	18.19	1-78	0-84
MFIS$_{Physical}$	18.73	19.5	9.22	0-36	0-36
MFIS$_{Cognitive}$	15.83	16	8.82	0-34	0-40
MFIS$_{Psychosocial}$	3.71	4	2.16	0-8	0-8
PHQ-9**	5.74	4	4.64	0-19	0-27
PDQ$_{Total}$	26.57	26	15.93	0-67	0-80
PDQ$_{Attention/Concentration}$	7.67	8	4.43	0-16	0-20
PDQ$_{Retrospective\ Memory}$	6.90	6	4.66	0-17	0-20
PDQ$_{Prospective\ Memory}$	5.63	5	3.50	0-17	0-20
PDQ$_{Planning/Organization}$	6.17	6	4.16	0-15	0-20

** MFIS total scores of 38 or higher represent fatigued individuals (Larson et al., 2013).*

***PHQ-9 total scores of 10 or higher have an 88% sensitivity and specificity for major depression (Kroenke et al., 2001).*

Relationship Between Physical Activity and MS Symptoms

There was a significant negative relationship between GLTEQ scores and MFIS scores; this relationship continued to be significant when controlling for age (Table 1.3). When the MFIS scores were broken down into 3 subscales: MFISphysical, MFIScognitive, and MFISpsychosocial, both the MFISphysical and MFISpsychosocial scores were negatively related to GLTEQ scores. Similarly, there

was a negative significant relationship between GLTEQ scores and PHQ-9 scores; this relationship continued to be significant when controlling for age (Table 1.3). The relationship between GLTEQ scores and PDQ scores were not significant (Table 1.3). When the GLTEQ was broken down into 4 subscales: PDQattention/concentration, PDQretrospective memory, PDQprospective memory, PDQplanning/organization, PDQretrospective memory and PDQprospective memory scores were negatively related to GLTEQ scores, and continued to be significant when controlling for age. The same pattern of relationships was observed in the separate group analysis for RRMS groups (Table 1.3). A similar pattern of relationships was also observed in progressive MS subtypes, however the progressive MS subtypes group did not reach statistical significance (Table 1.3).

Table 1.3. *Spearman Correlation and Partial Correlation Coefficients for the Relationship Between Physical Activity, Assessed Using the Godin Leisure-Time Exercise Questionnaire (GLTEQ), and Self-Report Questionnaires Related to Fatigue (Modified Fatigue Impact Scale; MFIS), Mood (Patient Health Questionnaire; PHQ-9) and Perceived Cognitive Impairment (Perceived Deficits Questionnaire; PDQ) in Individuals with MS, Relapsing Remitting MS (RRMS), and Progressive MS (PPMS/SPMS) Subtypes.*

			All N=86		RRMS N=58		Progressive(PPMS/SPMS) N= 24	
Questionnaire	Correlation with GLTEQ	p	Partial correlation*	p	Partial correlation*	p	Partial correlation*	p
MFIS$_{Total}$	-.36	< .001	-.34	.002	-.31	.02	-.30	.16
MFIS$_{Physical}$	-.41	<.001	-.38	<.001	-.32	.01	-.35	.10
MFIS$_{Cognitive}$	-.21	.05	-.20	.07	-.19	.16	-.21	.33
MFIS$_{Psychosocial}$	-.36	<.001	-.33	<.001	-.29	.03	-.20	.35
PHQ-9	-.23	.03	-.23	.03	-.23	.07	-.14	.51
PDQ$_{Total}$	-.19	.08	-.19	.08	-.23	.08	.02	.92
PDQ$_{Attention/Concentration}$	-.08	.47	-.08	.49	-.12	.34	.16	.46
PDQ$_{Retrospective\ Memory}$	-.24	.03	-.24	.03	-.28	.03	-.04	.86
PDQ$_{Prospective\ Memory}$	-.22	.04	-.22	.04	-.25	.06	-.06	.79
PDQ$_{Planning/Organization}$	-.17	.11	-.16	.13	-.19	.16	.03	.90

**Controlling for age*

Discussion

The current study examined the relationship between physical activity (GLTEQ) and fatigue (MFIS), mood (PHQ-9), and perceived cognitive impairment (PDQ) in 86 individuals with MS. As hypothesized, there was a significant negative relationship between physical activity and both fatigue and depression scores. There was not a significant relationship between physical activity and overall perceived cognitive impairment, however, there was a significant relationship between physical activity and perceived retrospective memory impairment and perceived prospective memory impairment. Follow-up separate group analyses were explored for individuals with RRMS and individuals with progressive MS. Although a similar pattern of relationships was evident in the separate group analyses for individuals with RRMS, the same relationships did not reach statistical significance for progressive MS. However, given the small number of individuals who reported a progressive subtype, it is important to note that this follow-up subgroup analysis had insufficient power.

Fatigue

Fatigue is among the most common symptoms of MS, as it is noted by up to 80% of individuals with MS (Zajicek et al., 2010; Heine et al., 2015). The current study found that more frequent or strenuous physical activity is associated with less reported fatigue. This finding is congruent with a recent Cochrane review of 36 studies (Heine et al., 2015), which found preliminary evidence that exercise reduces the amount of self-reported fatigue. Of these studies, 4 used MFIS subscale scores to

further explore the relationship between exercise and the impacts of fatigue. Exercise had a significant negative relationship with the physical impacts of fatigue in 3 of the studies, with cognitive impacts of fatigue in 2 of the studies, and with psychosocial impacts in 1 of the studies (Carter et al., 2014; Dodd et al., 2011; Garret et al., 2012). Similarly, other systematic reviews (e.g., Latimer-Cheung et al., 2013) report promising findings in support of exercise interventions for fatigue management but note that there is insufficient data to characterize an optimal level of prescribed physical activity. Although further experimental work on larger samples is required, the current findings provide support for the negative relationship between physical activity and fatigue.

Mood

Up to 50% of individuals with MS experience co-morbid depression at some point in their lives (Feinstein et al., 2014). Pharmacological treatment of depression in MS is often minimally effective in reducing symptoms and has been associated with adverse side effects (Koch et al., 2011). The current study found that more frequent or strenuous physical activity is associated with fewer depressive symptoms. This finding is in agreement with a recent meta-analysis of 13 randomized controlled trials that found small, but significant effects of exercise training on improving depressive symptoms (Ensari, Motl, & Pilutti, 2014). Other meta-analyses have found more heterogeneous results, with approximately 33% of studies finding a pattern similar to the current findings, and 66% of studies observing no effect of physical activity on depression (Dalgas, Stenager, Sloth, & Stenager, 2015). It is likely that a number of methodological limitations contribute

to these mixed findings; factors including varied physical activity interventions, diverse outcome measures (where depression is not a primary outcome measure) and small sample sizes may each play a role (Feinstein, Rector & Motl, 2013).

Cognitive Impairment

Up to 70% of individuals with MS experience cognitive impairment (Planche et al., 2016). The current study did not find significant evidence that physical activity influenced an individuals' overall perceived cognitive function. However, when the PDQ subscales were examined separately, physical activity was associated with perceived retrospective and prospective memory. This stands in contrast to a study (Prakash, Snook, Kramer, & Motl 2010) that observed significant negative relationships between physical activity, as assessed by GLTEQ, and overall perceived cognitive impairment, attention/concentration, and planning/organization, (but not prospective or retrospective memory subscales), as assessed by the PDQ, in individuals with RRMS. Still, other studies that have employed more objective measures of memory using neuropsychological tests and/or imaging hippocampal volume have found preliminary evidence that physical activity may be associated with greater memory performance (e.g., Leavitt et al., 2014; Sandroff, Johnson & Motl, 2017).

This brings forth an important consideration that individuals' perceived cognitive impairment might differ from their actual level of cognitive function (Strober et al., 2016). Given that the current study administered questionnaire measures via mail, no formal neuropsychological testing was completed. One systematic review of 7 studies found limited evidence that aerobic exercise

improves cognitive function based on neuropsychological tests, but this review included individuals with a number of neurological disorders (stroke, traumatic brain injury, Parkinson's disease, Alzheimer's disease, dementia) in addition to individuals with MS (McDonnell, Smith, & Mackintosh, 2011). A more recent systematic review of 26 MS studies (Sandroff, Motl, Scudder, & DeLuca, 2016a) found mixed evidence regarding cognitive outcomes (e.g., processing speed, attention, memory, executive function) when they examined exercise, physical activity, and fitness in individuals with MS. These mixed findings may have again resulted from methodological limitations. Although there was preliminary evidence of a positive effect of physical activity on cognition, there were insufficient well-designed studies that used cognition as a primary outcome measure.

Study Limitations and Future Directions

There are several limitations to the current study. First, the interpretation of results is limited by the study's correlational design. Although there was a significant relationship observed between physical activity and fatigue, depression, and perceived memory, conclusions regarding causation or directionality cannot be determined. Additionally, all of the measures were self-report, which are susceptible to biases such as an unwillingness to fully disclose information, or insufficient introspective ability to answer questions accurately. Although the mail out study method allowed for recruitment of a large number of individuals with MS in timely manner, no clinical interviews or neuropsychological testing was completed due to the nature of data collection. Furthermore, although all individuals enrolled within Island Health's permission to contact program had confirmed diagnoses of MS, their

MS subtype was self-reported. The type of physical activity that was performed also was not recorded in detail (the GLTEQ only requires that participants endorse frequency of exercise). Future research studies may benefit from including structured clinical interviews and neuropsychological tests for a more comprehensive evaluation of MS symptoms and comorbid psychological disorders.

Another limitation is that participant recruitment was limited to individuals residing on Vancouver Island and the Gulf Islands of British Columbia, Canada. These regions have a high proportion of Caucasian individuals with higher socioeconomic status, which may not be generalizable to the global MS population. Future research studies may benefit from multi-site data collection that recruits from a larger, more diverse participant pool. Previous literature has also shown that outcome may be influenced by MS clinical course (i.e., MS subtype, Planche et al., 2016). It would be especially useful for future studies to be explicit when reporting participant characteristics, including MS subtypes, and to be mindful of the distribution of their sample with respect to MS subtype when designing studies, analyzing data, and reporting findings. Notably, there were a small number of individuals who reported a progressive subtype of MS in this current study. Thus, it is likely that the follow-up analysis with progressive MS only had insufficient power. Future research will follow-up with larger groups of individuals with progressive MS in order to further explore these relationships. Finally, longitudinal designs are needed to capture the effects of physical activity over time.

Conclusion

In summary, individuals with MS who reported more strenuous and/or frequent physical activity, reported fewer problems with fatigue, depression, and perceived memory. Future research on the impact of physical activity as a behavioral treatment strategy should use an experimental design with fatigue, mood, and cognitive impairment as primary outcome variables. Additionally, groups with larger number of individuals with progressive MS is essential to better understand whether the impact of physical activity on psychosocial variables is influenced by MS clinical course (MS subtype).

Study Two: Are Physical Activity, Neuropsychological Performance, and Self-Reported Symptoms Related to Brain Structure in Relapsing-Remitting Multiple Sclerosis?

Abstract

Introduction: Multiple Sclerosis (MS) is a chronic disease of the central nervous system, which causes alterations in brain structure such as demyelination. Early investigations have shown that physical activity may hold promise for MS, but the extent to which physical activity may be neuroprotective is unclear. To date, few studies on physical activity with MS have included neuroimaging methods to assess brain structure. Therefore, the purpose of this study was to investigate whether reported physical activity, neuropsychological performance, and common MS symptoms of fatigue and depressed mood were related to white matter microstructure using diffusion tensor imaging (DTI). **Method:** Fourteen individuals with relapsing-remitting MS participated in this study. Each individual completed the Godin Leisure-Time Exercise Questionnaire (GLTEQ) to assess current level of mild, moderate, and strenuous physical activity, the Symbol Digits Modalities Test (SDMT) to assess cognition, the Modified Fatigue Impact Scale (MFIS) to assess fatigue, and the Beck Depression Inventory, 2nd edition (BDI-II) to assess mood. 3T diffusion weighted images were also collected to assess white matter microstructure. Image pre-processing and data analyses were performed in FMRIB Software Library. Tract-based spatial statistics was used to generate metrics of white matter microstructure, including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD). **Results:** There were no significant relationships between any of the examined DTI metrics (FA, MD, AD, RD) and the GLTEQ scores related to total physical activity or moderate-to-strenuous physical activity. Additionally, there were no significant relationships between DTI

metrics and SDMT, MFIS, or BDI-II scores. **Conclusions:** There was no evidence of a direct relationship between white matter microstructure and physical activity for individuals with RRMS, nor was there evidence for a direct relationship between white matter microstructure and MS symptoms related to cognition, fatigue, and mood.

Introduction

Multiple Sclerosis (MS) is a chronic disease of the central nervous system, which causes alterations in brain structure including demyelination (Lassman, 2018). Focal areas of myelin loss, called lesions can be distributed across the central nervous system, leading to a variety of MS symptoms (Popescue et al., 2013; Thompson et al., 2017). In addition to frequently recognized sensory and motor symptoms (Compston & Coles, 2008), individuals with MS can also commonly experience symptoms such as changes in cognition, fatigue, and depressed mood. Indeed, up to 70% of individuals with MS experience cognitive impairment (Planche et al., 2016), up to 50% experience depression (Feinstein et al., 2014), and up to 80% experience fatigue (Wood et al., 2012; Zajicek et al., 2010).

Physical activity holds promise for the management of some MS symptoms (e.g., Rietberg et al., 2005, Motl & Pilutti, 2012). Previously, our group found that individuals with MS who reported more strenuous and/or frequent physical activity reported fewer perceived memory problems, and less fatigue and depression (Mayo et al., 2019). These findings were consistent with meta-analyses that have found that exercise training with MS is associated with reductions in fatigue (Pilutti et al., 2013) and depression (Dalgas et al., 2015).

What remains unclear is the extent to which physical activity is related to brain structure in MS because neuroimaging studies related to physical activity in MS are rare (Giesser 2015; Motl & Sandroff, 2015). In a single case study, increases in hippocampal volume were observed following a 30-minute aerobic exercise intervention (3 times a week for 3 months) using 3T structural magnetic resonance

imaging (MRI; Leavitt et al., 2014), providing early evidence that exercise may be neuroprotective in MS.

While conventional MRI is routinely used in the diagnostic workup for MS (Thompson et al., 2017) and to monitor subsequent disease progression (Filippi et al., 2011), there has been increasing interest in quantitative MRI methods such as diffusion tensor imaging (DTI). DTI provides information about water diffusion within tissues in the brain, allowing for characterization of microstructural white matter changes that are observable sooner compared to conventional MRI (Alexander et a., 2007; Commowick et al., 2008).

Few studies have used DTI to investigate the relationship between exercise and white matter integrity in MS, despite white matter degeneration being the key feature of the disease (Lassman, 2018). Of particular relevance to the current study, an early study that used DTI found that higher cardiorespiratory fitness was associated with higher FA values in the left posterior thalamic radiation, optic radiation, right anterior corona radiata, genu of the corpus callosum (Prakash et a., 2010). More recently, another study used DTI to investigate whether an active motor rehabilitation intervention (20 one-hour sessions, three times per week) could improve motor ability in individuals with MS (Bonzano et al., 2014). Results showed that white matter integrity in the corpus callosum and corticospinal tracts were preserved in the group who participated the rehabilitation treatments, compared to a gradual worsening of white matter integrity (decreased FA and increased RD) observed in an MS control group who participated in passive mobilization treatments.

Given the paucity of studies employing DTI, the primary goal of this study was to investigate whether reported level of physical activity was related to white matter microstructure using DTI in individuals with relapsing-remitting MS (RRMS). Additionally, DTI was also used to determine whether neuropsychological performance and common self-reported symptoms of fatigue and depressed mood were related to white matter microstructure. It was hypothesized that individuals with RRMS who reported more frequent and strenuous physical activity may have higher white matter integrity, perform better on a neuropsychological processing speed test, and report fewer MS-related symptoms (less fatigue-related symptoms, less depressive symptoms).

Methods

Participants

Potential participants were recruited using Island Health's Permission to Contact program, which connects eligible researchers with individuals with a declared interest in research participation. All recruited participants were individuals diagnosed with RRMS, who were 19 years of age or older, fluent in English, and able to walk without assistance or rest for 300 meters or more. Individuals who had MRI contraindications (e.g., metal implants) or pre-morbid neurological conditions were not eligible to participate.

The current study was approved by the Harmonized Research Ethics Board at the University of Victoria and Island Health.

Imaging Data Acquisition

Imaging data were collected on a 3T GE Signa Pioneer MRI scanner using an axial echo planar imaging sequence with these parameters: TR = 8000 ms, TE = 101 ms, flip angle = 90°, 52 slices, voxel size = 1.4 x 1.4 x 2.0 mm. Acquisition time = 6 minutes. There were 48 images acquired for each scan: 45 diffusion-weighted images (b = 1000 s/mm^2) and 3 non-diffusion-weighted images (b = 0 s/mm^2).

Physical Activity

The Godin Leisure-Time Exercise Questionnaire (GLTEQ; Godin & Sheppard, 1985; Godin, 2011) was used to assess physical activity. The GLTEQ is a measure of self-reported physical activity over the past week and has been validated for use in MS populations (Gosney et al., 2007; Motl, Bollaert, & Sandroff, 2018). See Appendix D for psychometric properties. In the GLTEQ, respondents are asked to report the frequency of mild, moderate, and strenuous physical activity in the last 7 days (with a duration of at least 15 minutes).

Neuropsychological Processing Speed Testing

The Symbol Digit Modalities Test (SDMT; Parmenter et al., 2007) was used to assess cognition. The SDMT is a timed pencil and paper-based neuropsychological test that requires participants match numbers to geometric figures as quickly as possible. It is considered the gold standard for assessing cognitive processing speed in MS and has been found to be the most sensitive individual test for assessing cognition in MS (Strober et al., 2018).

Self-Report Measures

The Modified Fatigue Impact Scale (MFIS) of the MS Quality of Life Inventory (Fisk et al., 1994; Ritvo et al., 1997) was used to assess fatigue. In the MFIS, respondents are asked to rate how often they are impacted by physical, cognitive, and psychosocial fatigue ("never" to "almost always") over the past four weeks.

The Beck Depression Inventory, 2nd edition, (BDI-II; Beck et al., 1996) was used to assess mood. For each question, respondents of the BDI-II are asked to select one statement out of four that best describes how they have been feeling over the past two weeks.

Image Preprocessing

All MRI images were pre-processed using FMRIB Software Library (FSL; Smith et al., 2004). First, eddy current distortions and head movement were corrected (Eddy Correct). Second, non-brain tissue was removed (Brain Extraction Tool) and visually inspected to ensure no brain tissue was removed (Smith et al., 2002). Third, fractional anisotropy (FA) maps were generated using DTIfit and input into Tract-Based Spatial Statistics (TBSS) to obtain a projection of all participants' FA data onto a mean FA skeleton (Smith et al., 2006). To do so, first, all participants' FA data were non-linearly aligned to common space. Second, the mean FA image was created a thinned (threshold = 0.2) to create a mean FA skeleton. Third, each participant's FA data was projected on to the thresholded mean FA skeleton before applying voxelwise statistics. TBSS was also performed for mean diffusivity (MD); non-linear registration was applied to MD data, and then all participants' MD data was merged into a 4D file. Each participant's MD data was projected onto the mean

FA skeleton before applying voxelwise statistics. This process was also repeated for axial diffusivity (AD), and radial diffusivity (RD).

Scoring Neuropsychological Processing Speed Testing and Self-Report Measures

Two scores were calculated for the GLTEQ. First, the weekly frequency of mild (e.g., yoga), moderate (e.g., fast walking), and strenuous (e.g., running) physical activity was multiplied by 3, 5, and 9 respectively, and then summed to yield a total score (GLTEQtotal). Second, the weekly frequency of moderate and strenuous physical activity was multiplied by 5 and 9 respectively, and then summed to yield the GLTEQ "health contribution score" (GLTEQ-HCS). The GLTEQ-HCS is a newly derived score thought to best reflect the physical activity that confers a substantial health benefit (Godin, 2011). The GLTEQ-HCS has recently been validated for use in MS populations (Motl et al., 2018). SDMT raw scores were summed and then normed for age, sex, and education. Raw scores were also summed to obtain the total score for MFIS and BDI-II. Group-level descriptive data were generated using R Studio.

Statistical Analysis

Voxel-wise statistical analysis was performed using Randomise, FSL's nonparametric permutation inference tool, with threshold free cluster enhancement ($p < 0.05$, corrected for multiple comparisons). Relationships between DTI metrics (FA, MD, AD, RD) and GLTEQ scores (GLTEQtotal and GLTEQ-HCS), SDMT, MFIS, and BDI-II were each examined. All significant white matter regions were to be

identified with Johns Hopkins University's white matter atlas included in FSL (Mori et al., 2008; Wakana et al., 2007).

Results

Participants

Sixteen individuals with RRMS were recruited for the study. One individual withdrew prior to study completion. Another individual's DTI scans were not properly acquired, and thus, were not included in the analysis. Remaining participants included 11 females and 3 males with RRMS (mean age = 57.98 ± 11.10 years; mean education = 15.00 ± 2.08 years).

Physical Activity

Descriptive statistics for the GLTEQtotal and GLTEQ-HCS are reported in Table 2.1. There were no significant relationships between any of the examined DTI metrics (FA, MD, AD, RD) and the GLTEQtotal or the GLTEQ-HCS ($p < 0.05$, corrected for multiple comparisons).

Table 2.1. *Descriptive statistics for the Godin Leisure-Time Exercise Questionnaire (GLTEQ) for physical activity that is mild, moderate, and strenuous (GLTEQtotal) and moderate and strenuous only (GLTEQ-HCS).*

Measure	Mean score	Median score	Standard deviation	Observed Range	Possible Range
$GLTEQ_{total}$	29.29	26.50	20.73	3-77	≥0
$GLTEQ\text{-}HCS^{1}$	18.79	12.50	21.01	0-71	≥0

[1]GLTEQ-HCS scores of 0-14 = insufficiently active, 14-23 = moderately active, 24+ = active (Godin, 2011).

Cognition, Fatigue, and Mood

Descriptive statistics for the SDMT, MFIS, and BDI-II scores are reported in Table 2.2.

Table 2.2. *Descriptive statistics for the Symbol Digit Modalities Test (SDMT), Modified Fatigue Impact Scale (MFIS), and Beck Depression Inventory (BDI-II).*

Measure	Mean score	Median score	Standard deviation	Observed Range	Possible Range
SDMT[1]	48.85	55.50	21.78	16-94	0-99%tile
MFIS[2]	32.60	32.50	14.31	14-59	0-84
BDI-II[3]	8.60	7.50	8.14	0-28	0-63

[1]Reported as percentiles. A score of 60 = score equal to or greater than 60% of respondents of the same age, education, sex

[2]MFIS total scores of 38 or higher represent fatigued individuals (Larson et al., 2013)

[3]BDI-II total scores of 0-13 = minimal depression, 14-19 = mild depression, 20-28 = moderate depression, 29-63 = severe depression (Beck et al., 1996)

There were no significant relationships between any of the examined DTI metrics (FA, MD, AD, RD) and SDMT scores ($p < 0.05$, corrected for multiple comparisons). Similarly, there were no significant relationships between any of the examined DTI metrics (FA, MD, AD, RD) and MFIS scores ($p < 0.05$, corrected for multiple comparisons). Additionally, there were no significant relationships between any of the examined DTI metrics (FA, MD, AD, RD) and BDI-II scores ($p < 0.05$, corrected for multiple comparisons.

Discussion

This study used DTI to investigate whether reported level of physical activity, neuropsychological performance, and self-reported symptoms of fatigue and depressed mood were related to white matter microstructure in individuals with

RRMS. It was hypothesized that individuals with RRMS who reported more frequent and strenuous physical activity may have higher white matter integrity, perform better on neuropsychological processing speed testing, and report fewer MS symptoms. Results indicated that there was not a significant relationship between DTI metrics (FA, MD, AD, RD) and either total physical activity (GLTEQtotal) or moderate-to-strenuous physical activity (GLTEQ-HCS). Furthermore, there was not a significant relationship between DTI metrics (FA, MD, AD, RD) and neuropsychological performance (SDMT), fatigue (MFIS) or mood (BDI-II).

Physical Activity

Significant widespread alterations in DTI metrics have been observed in individuals with MS (Preziosa et al., 2011; Sbardella et al., 2013), including lower FA and higher MD. The extent to which DTI metrics may be impacted by physical activity is unknown, but it is hypothesized that physical activity may aid in the maintenance of white matter microstructural integrity (Gons et al., 2013).

While the relationship between physical activity and white matter microstructure has not been well investigated within MS, numerous other studies have attempted to characterize this relationship in other populations; indeed, much of the literature in this realm has involved aging populations. A recent meta-analysis found that while there was some evidence that higher levels of physical activity was associated with higher white matter microstructure in aging populations, there were a number of studies who did not observe any significant relationships (Sexton et al., 2015). Of the six cross sectional MRI studies of white matter microstructure that had FA as an outcome measure, three found a positive relationship with

physical activity (Johnson et al., 2012; Liu et al., 2012; Tseng et al., 2013), while three found no such relationship (Burzynska et al., 2014; Tian et al., 2014a; Tian et al., 2014b). Similarly, of the three cross sectional MRI studies of white matter microstructure that had MD as an outcome measure, one found a negative relationship with physical activity (Tseng et al., 2013), while two found no significant relationship (Johnson et al., 2012; Marks et al., 2011). It is important to note that the diversity in findings may be partly attributed to diversity in research designs; for example, while some studies used physical activity questionnaires, like in the current MS study, others conducted fitness tests directly. Relatedly, there was diversity in the type, duration, and frequency of the physical activity, which is not uncommon among this literature, but can contribute to seemingly conflicting findings (Sandroff et al., 2016a).

Of the few investigations involving individuals with MS, Prakash and colleagues (2010) explored whether cardiorespiratory fitness (assessed using braked cycle ergometer to measure peak oxygen consumption) was associated with white matter integrity (assessed using FA). Results indicated that higher cardiorespiratory fitness was associated with higher FA values in the left posterior thalamic radiation, optic radiation, right anterior corona radiata, genu of the corpus callosum. Diffusivity metrics, including MD, AD, and RD were not explored in this study. While in contrast to the current study, it is notable that physical activity was assessed different capacities; Prakash and colleagues (2010) assessed through an in vivo fitness test, while the current study assessed using the GLTEQ, which may contribute, in part, to the differences in findings.

Overall, given the paucity of studies exploring the relationship between physical activity and white matter microstructure in MS in particular, more research is needed to better characterize these relationships. Studies seeking to establish causation, such as controlled exercise intervention studies will be particularly useful in investigating whether physical activity impacts brain structure longitudinally.

Cognition, Fatigue, and Mood

The SDMT is considered the gold standard test of cognition for MS (Strober et al., 2018). In the current study we did not observe a relationship between cognition (SDMT) and white matter microstructure (FA, MD, AD, RD). These findings stand in contrast to findings from a recent study, which found that lower SDMT scores were associated with widespread lower FA, and higher diffusivity metrics (MD, AD, RD) in 177 individuals with RRMS (Riccitelli et a., 2019). Given our relatively small sample size (N=14), it is possible that we were unable to detect these same relationships, especially given that the majority of our participants were not as cognitively impaired (with most performing at or above the 50th percentile).

Many MS studies have sought to determine the neuroanatomical white matter correlates of fatigue, with variable findings (Bisecco et al., 2016; Genova et al., 2013; Novo et al., 2018; Pardini et al., 2010, see Chalah et al., 2015 for a review). Recently, Novo and colleagues (2018) explored the relationship between MFIS scores and DTI metrics of FA and MD. Consistent with our findings, there were no significant relationships observed between MFIS and FA. However, in contrast to our findings, there was a significant relationship between MFIS and MD in widespread regions including the corona radiata, internal capsule, external capsule,

corticospinal tract, cingulum, corpus callosum, fornix, superior longitudinal fasciculus, superior fronto-occipital fasciculus, sagittal stratum, posterior thalamic radiation, cerebral peduncle, and uncinate fasciculus.

Studies seeking to determine the neuroanatomical white matter correlates of depressed mood are relatively pauce. Feinstein and colleagues (2010) used diffusion tensor imaging to compare white matter microstructure in individuals with MS (RRMS and progressive MS) who were and were not depressed (assessed using the BDI-II; with scores equal to or greater than 19 indicated depression). Results indicated that individuals with MS who were depressed had lower FA in the normal appearing white matter in the left anterior temporal lobe, and higher MD in the normal appearing white matter in the left anterior temporal lobe and right inferior frontal lesions. The current study did not observe any relationship between mood (BDI-II) and DTI metrics. However, it is notable that in contrast to Feinstein and colleagues (2010), our participants generally had minimal levels of depression (mean score = 8.6), with only 1 participant having a BDI-II score greater than 19. Thus, future studies may wish to recruit groups of participants with more variable mood (ranging from minimal to severe depression) to better establish the relationship between depressed mood and white matter integrity.

Study Limitations and Future Directions

This study has a number of key limitations. First, it is important to note that the current study only sought to explore the correlation between white matter integrity and physical activity, neuropsychological performance, and self-reported

MS symptoms; this does not allow for conclusions about causation nor directionality.

The study is also limited by a smaller sample size, with only individuals with RRMS. Studies with larger sample sizes that also include individuals with progressive forms of MS are needed to determine whether MS subtype influences the relationship between physical activity, cognition, and MS symptoms.

There are also a number of participant characteristics that may be unique to our sample. Notably, none of the participants were sedentary, the majority performed within the average range on the SDMT and reported minimal levels of depression.

This study also used self-report measures for the assessment of fatigue and mood, which can be susceptible to biases, such as an unwillingness or inability to answer questions accurately. Future studies may benefit from including a structured clinical interview or review of medical records for a more comprehensive evaluation of MS symptoms.

Additionally, information about physical activity was self-reported via questionnaire (GLTEQ), rather than measured directly with fitness tests. However, previous MS studies have shown concordance between GLTEQ reports and accelerometer measurements for moderate and strenuous physical activity (Motl et al., 2018).

Lastly, this study only explored the relationships between physical activity, neuropsychological performance, MS symptoms and white matter microstructure using DTI., It did not investigate whether there are any relationships with functional

brain imaging metrics (e.g., functional magnetic resonance imaging). Thus, future studies may wish to take a multi-modal approach.

Conclusion

There was no evidence that higher levels of physical activity was related to higher white matter microstructure integrity for individuals with RRMS, nor was there evidence of a relationship between white matter microstructure and neuropsychological performance or self-reported symptoms of fatigue and mood. Given the limitations associated with the correlational design of this study, limited sample size, and unique participant characteristics, additional studies are needed. Future studies may benefit from implementing a larger, multi-site, controlled exercise intervention to best establish whether exercise may impact brain structure or aid in symptom management longitudinally. Furthermore, future studies may wish to employ multi-modal imaging approaches that include both structural and functional assessments of the brain to further explore the relationship of these metrics with physical activity.

Study Three: A Pilot Study of the Impact of an Exercise Intervention on Brain Structure, Cognition, and Psychosocial Symptoms in Individuals with Relapsing-Remitting Multiple Sclerosis

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Abstract

Introduction: Despite pharmacological treatment, many individuals with Multiple Sclerosis (MS) continue to experience symptoms and medication side effects. Exercise holds promise for MS, but changes in brain structure following exercise have not been thoroughly investigated, and important cognitive and psychosocial variables are rarely primary outcomes. The aim of this pilot study was to investigate whether the implementation of a 12-week exercise intervention would improve white matter integrity in the brain, or cognition, symptoms of fatigue, and depressed mood for individuals with relapsing-remitting MS (RRMS). **Method:** Thirteen participants completed 12 weeks of speeded walking. Baseline and post-intervention testing included 3T diffusion tensor imaging (DTI) to assess white matter and neuropsychological testing to assess cognition, fatigue, and mood. Image pre-processing and analyses were performed in FMRIB Software Library. **Results:** Post-intervention, there were no significant changes in white matter compared to baseline. Post-intervention, individuals with RRMS performed significantly better on the Symbol Digits Modality Test, reported fewer perceived memory problems, and endorsed less fatigue. Performance was not significantly different on Trails or Digit Span and there were no significant changes in reports of mood. **Conclusion:** Although 12 weeks of speeded walking did not improve white matter integrity, exercise may hold promise for managing some symptoms of RRMS.

Introduction

Multiple Sclerosis (MS) is a chronic inflammatory disease characterized by focal white matter degeneration and changes in grey matter volume. Given that the lesions associated with MS can be distributed throughout the central nervous system, individuals with MS often experience a constellation of sensory, motor, and cognitive symptoms, as well as issues with fatigue and mood (Compston & Coles, 2008). Because there is currently no cure for MS, and individuals are typically diagnosed in early adulthood, most individuals require treatment for the majority of their lives (Kister et al., 2013). Pharmaceuticals are often prescribed for long-term medical management, but these are costly, and have variable effectiveness with possible unwanted side effects (Hartung et al., 2015; Torkildsen et al., 2016). Thus, there is a critical need for the implementation of low-cost and side effect free behavioral interventions to help with symptom management.

In addition to medical management, exercise holds promise for individuals with MS. Exercise has shown benefits in the prevention of cognitive decline in aging populations (Bherer, Erickson, & Liu-Ambrose, 2013) and in the management of other types of neurological disorders, such as Parkinson's Disease and Alzheimer's Disease (Svensson et al., 2015; Jang et al., 2017). Importantly, exercise interventions can be accessible (e.g., can be completed without expensive equipment; available to diverse socioeconomic populations) and are non-invasive (Heine et al., 2015).

To date, several reviews and meta-analyses have looked at the clinical impact of exercise interventions for individuals with MS. These studies have provided early evidence that exercise interventions have modest effects on improving some MS

symptoms (Rietberg et al., 2005; Motl & Pilutti, 2012), however, the primary outcomes of these studies have largely been confined to physical measures (e.g., walking, strength, mobility). There is preliminary evidence that exercise may contribute to small improvements in cognition (Sandroff et al., 2016a), fatigue (Heine et al., 2015; Pilutti et al., 2013), and mood (Dalgas et al., 2015), but these cognitive and psychosocial variables were often not the primary outcome measures.

Currently, a significant limitation in the literature relates to the lack of investigations on changes in brain structure that may result from exercise interventions and relate to improved symptoms of MS. Indeed, the use of neuroimaging techniques, such as magnetic resonance imaging (MRI), to examine the neural effects of exercise in individuals with MS has been identified as a major gap in the literature (Giesser et al., 2015; Motl et al., 2015). MRI is a non-invasive, safely repeatable technique that allows for the examination of brain structure and is typically used in the assessment and diagnosis of MS (Thompson et al., 2017). One landmark study performed by Leavitt and colleagues (Leavitt et al., 2014), found that 12 weeks stationary cycling (3 times per week) contributed to increased hippocampal volumes, increased resting-state functional connectivity, and improved memory performance.

To date, very few studies have examined diffusion tensor imaging (DTI) metrics pre-post exercise intervention. DTI is a type of MRI scan that measures water diffusion in the brain to provide indices of white matter integrity (Alexander et al., 2007; Soares et al., 2013). DTI's sensitivity to detect microstructural

characteristics of white matter makes it an ideal tool to examine possible neuroprotective effects of exercise on individuals with MS (Harrison et al., 2011).

The goal of the current pilot study was to examine whether the implementation of a 12-week speeded walking exercise intervention would improve white matter integrity (as measured by DTI), cognition, or symptoms of fatigue and depressed mood for individuals with relapsing-remitting MS (RRMS).

Methods

Recruitment

Participants were recruited from the local health authority's Permission to Contact program. The Permission to Contact program connects eligible researchers with individuals who have declared an interest in participating in research. Interested participants contacted the research team via telephone or email, and they were assessed for eligibility. Based on the largest sample available within both funding and access to MRI constraints, 16 individuals were recruited.

Participants

Participants were eligible if they were diagnosed with RRMS, at least 19 years of age, fluent in English, able to walk without assistance or rest for at least 300 meters (consistent with Expanded Disability Status Scale score of 4.5 or less), able to complete study tasks independently. Exclusion criteria included having any MRI contraindications (e.g., metal implants, pacemakers), claustrophobia, and any comorbid neurological disorders. All participants attended pre- and post-intervention MRI and interview appointments, where neuroimaging,

neuropsychological testing, and self-report measures were completed (See Figure 3.1).

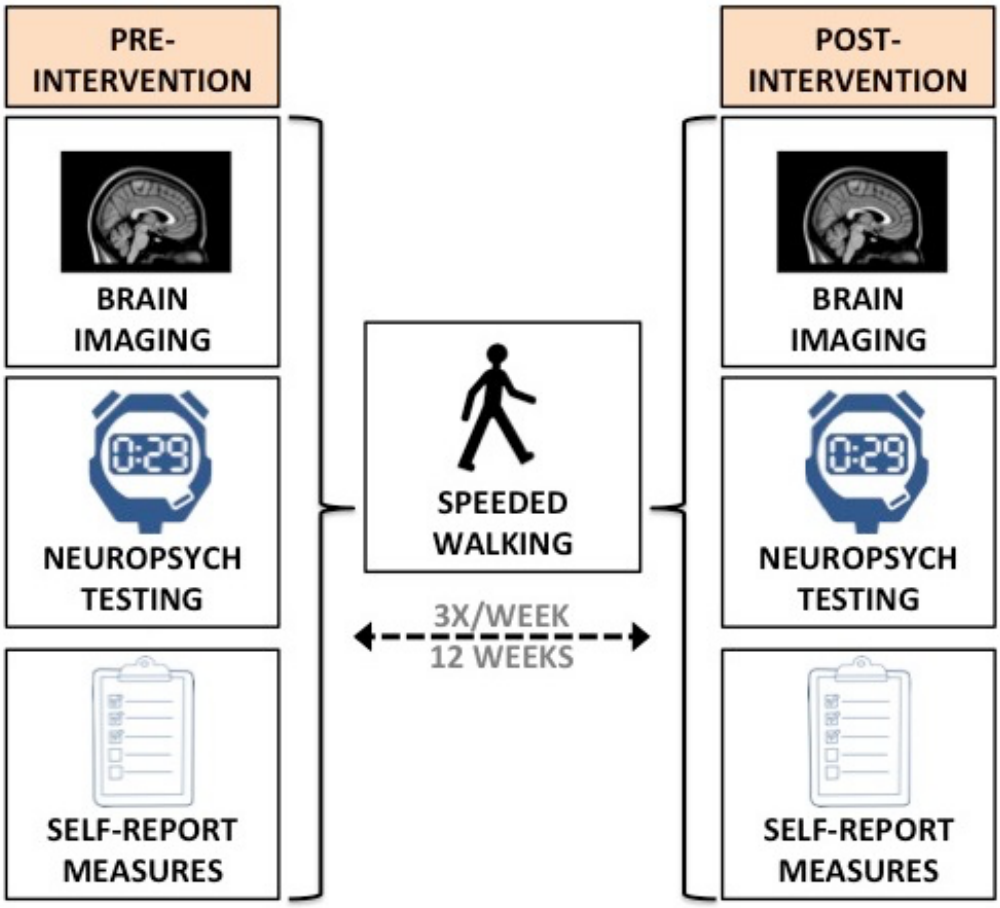

Figure 3.1. Study timeline; brain imaging, neuropsychological testing, and self-report measures were collected pre- and post- intervention.

Imaging Data Acquisition

DTI data was collected at West Coast Medical Imaging (Victoria, BC) on a 3T GE Signa Pioneer MRI scanner pre- and post- intervention. The images were acquired with an EPI sequence, axially, with the following parameters: TR = 8000 ms, TE = 101 ms, flip angle = 90°, 52 slices, voxel size = 1.4 x 1.4 x 2.0 mm. There were 48 images acquired for each scan: 45 diffusion-weighted images (b = 1000 s/mm^2) and 3 non-diffusion-weighted images (b = 0 s/mm^2). The acquisition took approximately 6 minutes.

Neuropsychological Testing and Self-Report Measures

Appointments took place at the University of Victoria. Pre- and post-intervention neuropsychological testing was conducted using the Symbol Digit Modalities Test (SDMT; Parmenter et al., 2007), Trail Making Test (Reitan, 1958) and Digit Span (Jensen & Figueroa, 1975; Wechsler, 2008) to assess cognition. Participants also completed pre- and post- intervention self-report measures to assess perceived cognitive impairment (attention/concentration, retrospective memory, prospective memory, and planning/organization; Perceived Deficit Questionnaire; PDQ; Ritvo et al., 1997) fatigue (Modified Fatigue Impact Scale; MFIS; Fisk et al., 1994; Ritvo et al., 1997), and mood (Beck Depression Inventory 2nd edition, BDI-II; Beck et al., 1988, 1996).

Speeded Walking Intervention

The exercise intervention, based on a treadmill walking intervention in a previous pilot trial (Sandroff et al., 2016b), involved speeded walking three times

per week at increasing intervals (15 to 35 minutes) over the course of 12 weeks (36 sessions total). Participants wore activity monitors and were asked to target a heart rate zone of at least 50% of maximum predicted heart rate and encourage adherence. They also logged their walking activity on an exercise tracking form provided to them. Participants were asked not to stop any consistent exercise (e.g., weekly class) in which they were already engaged, nor begin any new exercise that was unrelated to the study.

Data Analysis

Changes in DTI metrics (fractional anisotropy; FA, mean diffusivity; MD, axial diffusivity; AD, and radial diffusivity; RD), neuropsychological performance, and MS symptoms from pre- to post- intervention were examined. Image pre-processing and analysis was performed using FMRIB Software Library (Smith et al., 2004). Eddy Correct was used to correct for eddy current distortions and head movement. Next, Brain Extraction Tool was used to remove the non-brain tissue, and then brain-extracted images were visually inspected to confirm only non-brain tissue was removed (Smith et al., 2002). FA maps were generated using DTIfit and input into Tract-Based Spatial Statistics (TBSS; Smith et al., 2006), followed by Randomise with threshold-free cluster enhancement. This was repeated for MD, AD and RD. Non-imaging group-level demographic and inferential statistical analyses were performed in R Studio. Paired sample t-tests and Wilcoxon signed rank tests were used to compare post-intervention scores to pre-intervention scores on neuropsychological tests (SDMT, Trail Making Test, Digit Span) and self-report measures (MFIS, BDI-II, PDQ). Effect sizes were calculated using Cohen's *d* (paired t-

test) and matched rank biserial correlations (Wilcoxon). Normed (for age, education, and sex where available) neuropsychological test scores were used.

Results

Participants

Sixteen individuals with RRMS were recruited for the study, but three individuals withdrew prior to study completion. Remaining participants included 10 females and 3 males with RRMS (mean age= 58.76 ± 11.07 years; mean education= 15.15 ± 2.08 years). One female's imaging data was omitted from the DTI analysis due to missing post-intervention scans. Recruitment occurred in June 2018. Data collection took place from August 2018 to November 2018. Participants adherence was 98.29% (mean sessions completed = 35.38 ± 0.77 out of a total of 36 sessions).

DTI

Post-intervention there were no significant changes in any of the DTI metrics, including FA, MD, AD, or RD ($p<0.05$, corrected for multiple comparisons), compared to baseline. Extracted mean FA, MD, AD, and RD values are reported in Table 3.1.

Table 3.1. *Pre- and Post-Intervention Diffusion Tensor Imaging (DTI) metrics, Including Fractional Anisotropy (FA), and Mean, Axial, and Radial Diffusivity (MD; AX; RD; mm^2/s)*

Pre- Intervention DTI Metrics				Post-Intervention DTI Metrics			
FA	MD	AD	RD	FA	MD	AD	RD
0.436	0.00081	0.00121	0.00061	0.429	0.00081	0.00119	0.00061
0.499	0.00075	0.00119	0.00053	0.510	0.00073	0.00117	0.00051
0.508	0.00070	0.00112	0.00049	0.493	0.00071	0.00112	0.00051
0.520	0.00070	0.00115	0.00048	0.517	0.00071	0.00116	0.00049
0.483	0.00075	0.00118	0.00054	0.479	0.00075	0.00117	0.00054
0.503	0.00075	0.00122	0.00052	0.505	0.00074	0.00119	0.00051
0.495	0.00075	0.00119	0.00053	0.482	0.00075	0.00119	0.00054
0.498	0.00073	0.00117	0.00051	0.497	0.00074	0.00117	0.00052
0.477	0.00077	0.00120	0.00055	0.463	0.00078	0.00119	0.00057
0.477	0.00076	0.00118	0.00054	0.470	0.00076	0.00117	0.00055
0.516	0.00073	0.00119	0.00050	0.508	0.00073	0.00117	0.00050
0.489	0.00075	0.00119	0.00053	0.477	0.00076	0.00118	0.00054
0.492	0.00075	0.00118	0.00053	0.486	0.00075	0.00117	0.00053

Cognition, Fatigue, and Mood

Post-intervention, individuals with RRMS performed significantly better on the SDMT. Additionally, individuals with RRMS perceived fewer prospective memory problems (PDQ) and reported fewer symptoms of fatigue (MFIS) compared to pre-intervention. See Table 3.2.

Post-intervention performance on Trails A, Trails B, and Digit Span was not significantly different than pre-intervention performance. There were also no significant changes in reports perceived problems with attention, retrospective memory, or planning (PDQ) or mood (BDI-II) post-intervention compared to pre-intervention. See Table 3.2.

Table 3.2. *Pre- and Post-Intervention Performance on Neuropsychological Tests and Self-Report Measures*

	Pre- Intervention Scores				Post-Intervention Scores					
Neuropsychological Tests	Mean	Median	SD	Range	Mean	Median	SD	Range	p	Effect Size
SDMT	48.23	55	22.54	16-94	62.92	61	22.02	32-97	.002	-1.09
Trails A	69	82	31.20	4-95	74.92	82	20.27	25-96	.94	-.03
Trails B	64.85	81	35.10	.07-97	54.77	58	37.38	.07-98	.83	.08
Digit Span	41.31	50	20.98	5-75	48.77	50	29.66	2-91	.20	-.06
Self-Report Measures	Mean	Median	SD	Range	Mean	Median	SD	Range	p	
MFIS	32.31	30	14.86	14-59	25.53	29	12.75	7-42	.049	.61
BDI-II	8.54	5	8.46	0-28	5	3	4.36	0-13	.14	.52
PDQ	20.92	22	9.11	6-35	18.85	20	9.65	3-33	.31	.30
$PDQ_{Attention}$	7.23	7	3.24	2-13	6.62	7	3.33	1-12	.42	.23
$PDQ_{ProspectiveMemory}$	4.54	5	2.07	1-7	3.46	3	1.98	0-7	.02	.78
$PDQ_{RetrospectiveMemory}$	4.85	5	2.12	1-9	4.92	4	2.47	1-8	.91	.05
$PDQ_{Planning\&Organization}$	4.31	5	2.81	1-8	3.85	4	3.18	0-10	.52	.33

Discussion

This study investigated whether 12 weeks of speeded walking would significantly improve white matter integrity in the brain, cognition, or symptoms of fatigue and depressed mood for individuals with RRMS. Following 12 weeks of speeded walking, individuals with RRMS performed better on a cognitive measure involving processing speed, reported fewer perceived prospective memory problems and significantly less fatigue. There were no changes in white matter integrity, as measured by DTI.

Brain Changes

MS is characterized by demyelination and degeneration of axons, and the use of MRI is integral in clinical assessment and diagnosis (Thompson et al., 2017; Lassman, 2018). The current pilot study did not observe any white matter changes in individuals with RRMS following 12 weeks of speeded walking, as assessed using DTI. Although there were not significant improvements in white matter integrity, there were also no significant declines in white matter integrity, as may be expected in a demyelinating disorder such as MS (Lassman, 2018). Indeed, several studies have observed longitudinal changes in DTI metrics in individuals with MS over the course of weeks to years. For example, Bonzano and colleagues (2014) found that white matter DTI metrics in the corpus callosum and corticospinal tracts were preserved in an MS group who completed a 7-week active motor rehabilitation intervention, but found decreased FA and increased RD in these regions in an MS control group that participated in passive mobilization. Ontaneda and colleagues (2017) observed significant increases in AD in enhancing and chronic lesions over 4

years of follow up. Additionally, Kolasa and colleagues (2019) found increases in FA and AD and decreases in RD in regions of the corpus callosum over 4 years of follow up.

Changes in brain structure and function following exercise interventions, specifically, have not yet been thoroughly investigated in individuals with MS (Motl & Sandroff, 2015). Although there have only been a few pilot trials (Leavitt et al., 2014; Sandroff et al., 2016b) even fewer have used DTI. Recently, Tavazzi and colleagues (2018) used TBSS, among other imaging measures, to assess any differences in DTI metrics in 29 individuals following 4 weeks of rehabilitation exercises for MS that involved resistance or endurance training. Similar to our findings, there were no changes in any DTI metrics. Interestingly, they observed increased functional connectivity in the precentral and post-central gyrus at the end of the 4 weeks, but these findings did not hold at a second follow up three months later. Future research in this area would benefit from the use of multi-modal imaging approaches, including functional MRI, DTI and other structural imaging methods (e.g. T1 and FLAIR scan), to gain a more complete understanding of possible changes in the brain resulting from exercise intervention.

Cognition

Up to 70% of individuals with MS experience reductions in cognition, especially for tasks that involve information processing, executive function, and memory (Benedict & Zivadinov, 2011; Chiaravalloti & DeLuca, 2008; Planche et al., 2016). The current study found that individuals with MS performed significantly better on the SDMT following 12 weeks of speeded walking, but not Trails or Digit

Span. The SDMT is considered the measure of choice for MS as it has shown to be sensitive to declines in cognition observed in MS and has correlated well with other measures of disease progression, such as atrophy and lesion burden (Benedict et al., 2017; Strober et al., 2018). To date there are mixed findings on the impact of exercise on cognition in MS (Sandroff et al., 2016a); while some studies have found exercise improved performance on the SDMT (Sangelaji et al., 2015) other studies have found no such relationship (Briken et al., 2014; Motl & Sandroff, 2015). As in other psychosocial outcomes, this heterogeneity is possibly attributed to methodological issues, such as diversity in exercise interventions, and cognition not included as a primary outcome (Sandroff et al., 2016a). Efforts to reduce heterogeneity were made in the current study by choosing neuropsychological measures used frequently in MS research, and replicating an intervention used in a recent MS pilot trial (Sandroff et al., 2016b).

Fatigue

Fatigue is among the most commonly reported symptoms of MS (Bakshi, 2003; Asano & Finlayson, 2014). The current study found that individuals reported significantly less fatigue after 12 weeks of speeded walking. This result is consistent with findings from other meta-analyses (Pilutti et al., 2013). It is possible that exercise decreases pro-inflammatory cytokines, which are thought to be related to fatigue (Svensson et al., 2015; Heesen et al., 2005). Still, there is heterogeneity in findings, perhaps due to the variability in exercise interventions, ranging from endurance to strength training to mixed methods as well as fatigue being included as a secondary outcome measure (Heine et al., 2015).

Mood

Low mood is a common symptom of MS, and up to 50% of individuals diagnosed with MS have experienced depression at some point in their lifetime (Feinstein et al., 2014; Koch et al., 2015). The current study did not find evidence for significant reductions in reports of depressed mood following 12 weeks of speeded walking. However, it is important to consider that, this result may be particular to our study given that at baseline, the majority of participants reported minimal symptoms of depression. It is possible that the impact of exercise on mood may only be evident in individuals with more severe levels of depression. For example, in a meta-analysis, Dalgas and colleagues (2015) found that the studies that demonstrated positive impacts of exercise on mood in MS had participants with higher baseline levels of depression.

Study Limitations and Future Directions

As a pilot trial, the current study is limited by a small sample size, which is comprised exclusively of individuals with RRMS subtype, as has been common in research to date (Heine et al., 2015). The current study did not detect any structural white matter changes in the brain following the exercise intervention; this may be due, in part, to a limited sample size, but could also be influenced by additional factors (e.g., that the intensity or duration of the exercise was insufficient). Future research would benefit from larger samples that also include individuals with progressive forms of MS to help clarify this, as well as determine whether imaging, cognitive, and psychosocial outcomes are influenced by MS subtype. Future studies may also benefit from increasing the intensity of the prescribed aerobic exercise, as tolerated by individuals with MS, in

accordance with activity recommendations for individuals with MS (Latimer-Cheung et al., 2013; Dalgas et al., 2008).

The current pilot study also employed a within-persons pre-post design. As research in this area expands beyond pilot trials, the inclusion of additional control groups (i.e., individuals with MS who resume activity as normal) is needed to determine the extent to which exercise may impact the typical progression of pathological changes that occur in MS.

There are also a number of participant characteristics that may be unique to our participant sample. For example, it is also notable that some of our participants were already fairly active. Future research may choose to selective recruit sedentary participants to assess whether exercise has a greater impact for these individuals. Additionally, the majority of our participants were not cognitively impaired at baseline; many performed at or above the 50th percentile. Thus, future research may wish to specifically recruit individuals with cognitive impairment to better assess the impact of exercise on individuals with cognitive impairment.

Furthermore, the extent to which the observed improvements in fatigue and some aspects of cognition may be long lasting is unclear. It is possible that these improvements may eventually plateau, or otherwise decline across time. Thus, it would be useful for future research to track participants longitudinally over a number of years, with frequent follow-up appointments. Additionally, follow-up studies could use a design that captures change over time prior to the intervention, so this change can be compared to change over the course of the intervention. Importantly, given the traditional focus on physical measures (e.g., walking, strength, mobility)

future exercise research trials should consider including frequently observed psychosocial and cognitive symptoms as primary outcome measures.

Lastly, although the current study did not detect any structural white matter changes in the brain following the exercise intervention, it did not investigate whether any functional changes in the brain took place or whether there were changes in grey matter. There is preliminary evidence from other pilot trials that exercise interventions have contributed to increased resting state functional connectivity in the thalamo-cortical regions (Sandroff et al., 2018). Thus, future research would benefit from a multi-modal imaging approach that also include functional approaches such as functional MRI.

Conclusion

Following the implementation of a 12-week walking exercise intervention, individuals with RRMS performed significantly better on a measure of information processing speed, perceived fewer prospective memory problems and reported fewer problems with fatigue. White matter integrity did not significantly decrease or increase. Together this suggests that although there is not enough evidence to suggest speeded walking is reparative, 12 weeks of speeded walking holds promise for managing some symptoms for individuals with RRMS.

Concluding Remarks

The three studies in this manuscript-based dissertation sought to explore the *brain-based evidence for aerobic exercise as a treatment for Multiple Sclerosis (MS),* with a focus on cognitive, psychosocial, and diffusion tensor imaging (DTI) outcomes. The first study demonstrated that individuals with MS who reported more strenuous and/or frequent physical activity reported fewer problems with fatigue, depressed mood, and their perceived memory abilities. The second study did not find any evidence for a direct relationship between white matter microstructure in the brain (assessed using DTI) and physical activity for individuals with relapsing-remitting MS (RRMS), nor did it find any evidence for a relationship between white matter microstructure and MS symptoms related to cognition, fatigue, and mood. The third study demonstrated that although there were no significant increases or decreases in white matter structure following a 12-week exercise intervention, individuals with RRMS performed better on measures of information processing speed, reported fewer prospective memory problems, and reported fewer problems with fatigue. Together, these studies suggest that exercise may be useful in the management of some cognitive and psychosocial symptoms for individuals with RRMS, particularly with respect to fatigue and some aspects of cognitive impairment.

Moving forward, including individuals with progressive forms of MS will be important to determine whether cognitive and psychosocial outcomes are influenced by MS clinical course. Relatedly, multi-site longitudinal investigations with larger sample sizes are needed to determine whether improvements in MS

symptoms persist, plateau, or decline over time. The creation of a large, multi-site database with multi-year data would be especially useful. Finally, while the current studies did not detect changes in white matter microstructure, it did not explore whether there are any functional changes in the brain; thus, future investigations may benefit from a multi-modal imaging approach with the inclusion of functional methods (such as functional magnetic resonance imaging).

Critically, as research in this area progresses, we advocate for the continued involvement of individuals with lived experience in MS to serve in the role of consultants and/or team members on on-going research endeavors. In working alongside these individuals throughout the course of this dissertation, we were able to ensure that our research sought to answer relevant questions and include outcome measures that were both guided by current literature *and* meaningful to people affected by MS.

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Appendices

Appendix A

Multiple Sclerosis Lesions

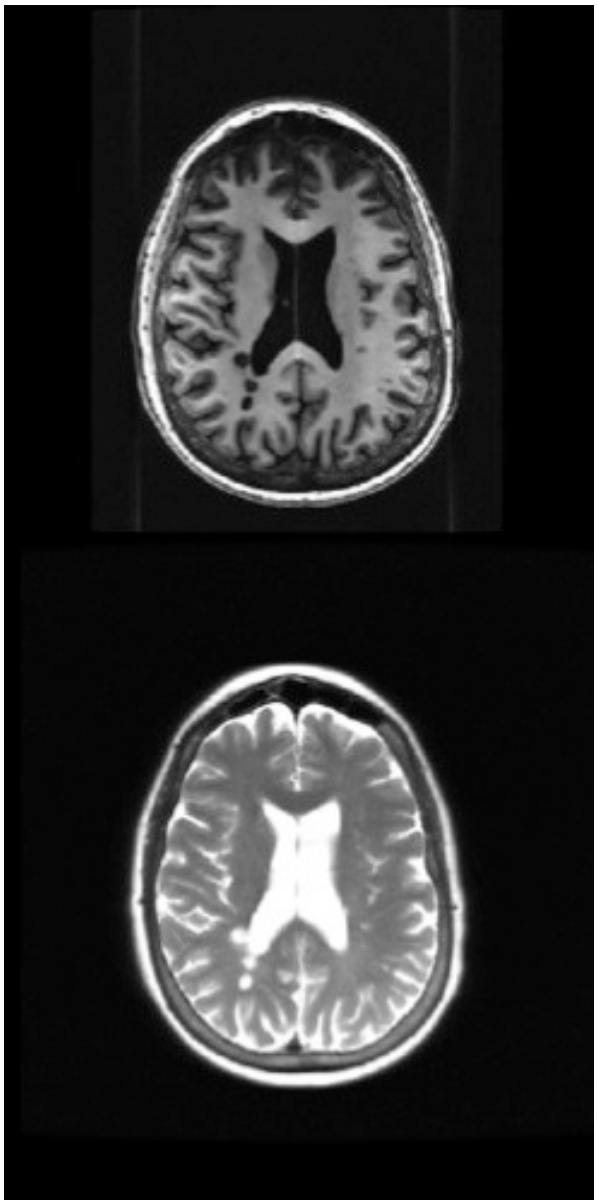

Figure A1. Brain of individual with Multiple Sclerosis with lesions visualized using T1-weighted (top) and T2 weighted (bottom) magnetic resonance imaging.

Appendix B

Multiple Sclerosis Diagnosis

Table B1. *The 2017 McDonald Criteria for Multiple Sclerosis.*

Number of Clinical Attacks[1]	Number of Lesions	Additional Data Required
2 or more	2 or more	*NA*
2 or more	1 plus objective historical evidence of previous attack involving a lesion in a distinct anatomical lesion.	*NA*
2 or more	1	Dissemination in space • Additional clinical attack in different central nervous system (CNS) site *or* • MRI[2]
1	2 or more	Dissemination in time[3] • Additional clinical attack *or* • MRI[3] *or* • Cerebrospinal fluid-specific oligoclonal bands
1	1	Dissemination in space *and* Dissemination in time

[1]A clinical attack is defined as, "a clinical episode with patient-reported symptoms and objective findings typical of MS, reflecting a focal or multifocal inflammatory demyelinating event in the CNS… with a duration of at least 24 hours." [2]The dissemination in space MRI criterion can be fulfilled by one or more T2-hyperintense lesions in at least two of four CNS regions including: periventricular, cortical/juxtacortical, infratentorial, and spinal cord. [3]The dissemination in time MRI criterion can be fulfilled by the presence of gadolinium-enhancing and non-enhancing lesions simultaneously or a new lesion with reference to a baseline scan.

Appendix C

Diffusion Tensor Imaging

Diffusion weighted magnetic resonance imaging is a neuroimaging method for characterizing microstructural white matter in the brain, based on water diffusion within brain tissues (Alexander et al., 2007; Commowick et al., 2008; Inglese & Bester 2010; Soares, Marques, Alves, & Sousa, 2013).

Diffusion patterns are influenced by the presence of biological barriers. Water that is not restricted by biological barriers diffuses equally in all directions; this is known as isotropic diffusion. In contrast, water diffusion can become restricted by biological barriers in the brain, and thus, diffuse in a directionally-dependent manner; this is known as anisotropic diffusion (Gold, 2012; Sbardella, Tona, Petsas, & Pantano, 2013; Soares et al., 2013).

In cerebrospinal fluid, diffusion is isotropic. In grey matter, barriers such as cell membranes partially restrict diffusion, but it is still largely isotropic. In contrast, diffusion is highly anisotropic in white matter. Because white matter is tightly organized into parallel fibre bundles, water is free to diffuse parallel to the direction of the axonal fibres orientation, but is restricted perpendicular to the fibres (Sbardella et al., 2013; Soares et al., 2013).

A diffusion tensor is a mathematical model of this water diffusion, acquired from at least 6 gradient directions (Jellison et al., 2004). Numerically, a diffusion tensor is represented by a diagonally symmetrical 3 by 3 covariance matrix (Alexander et al., 2007). Diagonalization of the covariance matrix generates three

eigenvectors (ε_1, ε_2, ε_3,) that represent the *direction* of maximum water diffusion and three corresponding eigenvalues (λ_1, λ_2, λ_3) that represent the *magnitude* of water diffusion in each vector (Alexander et al., 2007; Jellison et al., 2004). Visually, a diffusion tensor is represented by an ellipsoid shape (See Figure C1). When diffusion is isotropic, the eigenvalues are approximately equal, and the tensor is spherical. When diffusion is anisotropic, the eigenvalues are unequal and the tensor becomes elliptical (Alexander et al., 2007; Jellison et al., 2004).

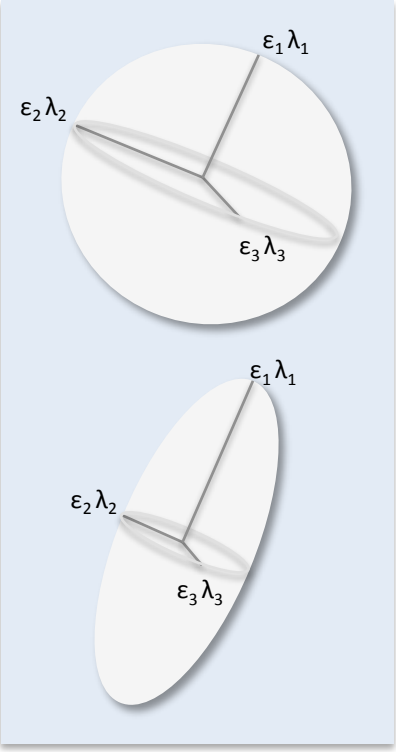

Figure C1. Top: Isotropic diffusion (eigenvalues λ_1, λ_2, λ_3 are equal). Bottom: Anisotropic diffusion (eigenvalues λ_1, λ_2, λ_3 are unequal).

Commonly reported diffusion tensor imaging (DTI) metrics used to describe microstructural characteristics in white matter are fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD; Alexander et al., 2007; Jellison et al., 2004).

FA

FA is a measure of the degree of directionality of the water diffusion, ranging from 0 (isotropic) to 1 (anisotropic). FA is calculated using the following formula:

$$FA = \sqrt{\frac{3}{2}}\sqrt{\frac{(\lambda_1 - \bar{\lambda})^2 + (\lambda_2 - \bar{\lambda})^2 + (\lambda_3 - \bar{\lambda})^2}{\left({\lambda_1}^2 + {\lambda_2}^2 + {\lambda_3}^2\right)}}$$

MD

MD is a measure of the water diffusion rate. It does not provide any information about the direction associated with the diffusion. A higher MD value reflects higher diffusivity (Sbardella et al., 2013). MD is calculated using the following formula:

$$MD = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}$$

AD

AD is a measure of the rate of water diffusion along the longitudinal axis (i.e., parallel to the fibre tracts). AD is calculated using the following formula:

$$AD = \lambda_1$$

RD

RD is a measure of the rate of water diffusion along the perpendicular axes. RD is calculated using the following formula:

$$RD = \frac{\lambda_2 + \lambda_3}{2}$$

Appendix D

Available Psychometric Properties of Measures Used in Studies 1, 2, and 3

Beck Depression Inventory, 2nd edition, (BDI-II; Beck et al., 1996)

The BDI-II has strong psychometric properties, including excellent internal consistency (α= 0.83-0.96) and good-to-excellent test-retest reliability (r= 0.73-0.96; Wang & Gorenstein, 2013). The BDI-II has previously been validated for use with individuals with MS (Watson et al., 2014).

Digit Span (Jensen & Figueroa, 1975, Wechsler 2008):

Digit Span has good internal reliability (α = 0.78-0.89; Wechsler, 2008) and test-retest reliability (r=0.71-0.77; Wechsler, 2008). It has previously been evaluated in relapsing-remitting MS, showing significantly worse performance compared to healthy controls (Ryan et al., 2012).

Godin Leisure Time Exercise Questionnaire (GLTEQ; Godin & Sheppard, 1985; Godin, 2011):

The GLTEQ is a valid and reliable self-report measure of physical activity for individuals with MS (Gosney et al., 2007; Sikes et al., 2019). The GLTEQ has been shown to have adequate test-retest reliability in MS populations (r= 0.74) and is moderately correlated with total activity as measured by an accelerometer (r=0.383-0.437; Motl, McAuley & Klaren, 2014).

Modified Fatigue Impact Scale (MFIS; Fisk et al., 1994; Ritvo et al., 1997):

The MFIS has good to excellent internal consistency, for total, cognitive, physical, and psychosocial scores (α = 0.81, 0.95, 0.91, 0.81 respectively; Larson et al., 2013; Ritvo et al., 1997). It is recommended for use for individuals with MS and included in the MS Quality of Life Inventory outcome assessment battery developed by the National MS Society and Consortium of MS Centres (Ritvo et al., 1997).

Perceived Deficit Questionnaire (PDQ; Ritvo et al., 1997):

The PDQ has good to excellent internal consistency for total, attention, retrospective memory, prospective memory, and planning/organization scores (α = 0.93, 0.82, 0.86, 0.74, 0.85 respectively; Ritvo et al., 1997). It is recommended for use in MS populations and included in the MS Quality of Life Inventory outcome assessment battery developed by the National MS Society and Consortium of MS Centres (Ritvo et al., 1997).

Patient Health Questionnaire 9 (PHQ-9; Kroenke, Spitzer, & Williams, 2011):

The PHQ-9 has been validated for use for individuals with MS (Amtmann et al., 2014; Patten et al., 2015; Patrick & Connick, 2019). When used as a screening tool for depression with a cut-off score of 11, it had 95% sensitivity and 88.3% specificity (Patten et al., 2015). It has also been shown to be correlated with other common measures of depression, including the Center for Epidemiological Studies Depression Scale-10 (r=0.85; Amtmann et al., 2014), and the Hospital Anxiety and Depression Scale (0.72; Patten et al., 2015). The internal consistency of the PHQ-9

(measured using item-total correlations in an MS population) ranges from r= 0.35-0.67 (Amtmann et al., 2014).

Symbol Digit Modalities Test (SDMT; Parmenter et al., 2007):

The SDMT is the gold standard for assessing cognitive processing speed in MS and is the most sensitive individual test for assessing cognition in MS (Strober et al., 2018). Test-retest reliability is excellent (r= 0.98 in group of individuals with MS; Benedict 2005). It is correlated with other measures of processing speed, including the Paced Auditory Serial Addition Test (r=0.54; Strober et al., 2018). The SDMT has been included in many recently developed MS cognitive test batteries, including the Minimal Assessment of Cognitive Function in MS (Benedict et al., 2017).

Trail Making Test (Reitan, 1958):

The Trail Making Test has adequate test-retest reliability in healthy (r=0.70 for A and B; Levine et al., 2004) and neurological populations (r=069 for A and 0.66 for B;Goldstein & Watson, 1989). It is frequently used when assessing cognition in MS (Costa, Genova, DeLuca & Chiaravalloti, 2017; Kirac, Ekmekci, Yuceyar, & Locaman, 2014).