Patient-Reported Cognition in People with Multiple Sclerosis: Neuropsychological Correlates and its Association with Cardiorespiratory Fitness

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Abstract

Cognitive impairment (CI) is a common manifestation of multiple sclerosis (MS). Physical activity and exercise training are promising approaches to address impairments and preserve function in people with MS; however, their potential effects on patient-reported cognition remain understudied. Patient-reported outcomes (PROs) may provide insight into the effects of MS and interventions that are not always detectable using objective assessments. The objectives of this thesis were to better understand: i) the neuropsychological utility and interpretation of cognitive PROs; and ii) the potential protective effects of maintaining physiological fitness (as a marker of physical activity and exercise) in people with MS.

Study 1 examined associations between cognitive PROs/insight (i.e., self-awareness of deficit) and objective neuropsychological outcomes (cognitive performance, biomarkers of neuroaxonal degeneration) and putative confounds (e.g., depression, fatigue). Analyses found that, in participants with MS, cognitive PROs more strongly correlated with the most affected objective neuropsychological outcomes in comparison to less affected outcomes. In the MS group, insight was not related to depression or fatigue. These preliminary findings provide support for the use of cognitive PROs to monitor/screen for MS-related cognitive decline.

Study 2 assessed the relationship between cardiorespiratory fitness (CRF) and cognitive PROs. Analyses found that higher CRF coincided with "overestimation" of CI in the MS group. There were no true CI underestimators in the MS sample, namely, persons with objectively measured CI who overestimate their cognitive function. This might explain why CI "overestimators" – who had unimpaired executive function – displayed the greatest biomarker evidence of neurodegeneration and slowest information processing speeds relative to participants with MS who accurately estimated/"underestimated" their CI. Because of this unique profile, the association that occurred exclusively in the MS sample between CRF and overestimation of CI was viewed as preliminary support for CRF being associated with heightened insight of the cognitive effects of MS.

The presented findings offer some support for the use of cognitive PROs to assess cognitive functioning in MS. Physical activity, exercise training, and the related maintenance of CRF may represent an approach for preserving cognitive precursors to insight in MS. Research is needed to replicate study findings in larger, more diverse MS samples. Future studies should examine longitudinal associations between cognitive PROs/insight and other objective neuropsychological outcomes in people with MS. Research should attempt to identify other components of fitness related to insight and elucidate what features of physical activity/exercise training may contribute to the preservation of insight in people with MS.

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Preface

The present thesis is a result of collaborative efforts between members of a larger, ongoing project. Ethics approval for the overarching project was obtained from the University of Ottawa research ethics board prior to commencing data collection. Dr. Arthur Chaves and Dr. Lara Pilutti conceptualized the design of the primary study, with the author (Aidan Peters) contributing the addition of patient-reported outcomes of cognition into the conceptualization of this main study. Dr. Arthur Chaves was primarily responsible for the overall study organization. Dr. Arthur Chaves, Ms. Katie Lindale, and Ms. Julia Ludgate were primarily responsible for participant recruitment, screening, and scheduling. Concerning the baseline data collection, Dr. Arthur Chaves, Ms. Julia Ludgate, and the author completed this component of the project. Ms. Shida Pourlotfi and the author completed data entry and checking. Dr. Arthur Chaves processed the cardiopulmonary exercise testing data. Retinal scans were evaluated by the author in accordance with quality criteria. Algorithmically generated retinal segmentation errors were manually corrected by the author. Cognitive tests were scored by the author.

The research questions and hypotheses addressed in the following text were developed by the author with inputs from Dr. Lara Pilutti. Data analyses were performed by the author under the guidance of Dr. Lara Pilutti. Chapters 1-5 were written by the author with feedback provided by Dr. Lara Pilutti and the thesis advisory committee members, Drs. Lindsay Berrigan, Erin Cressman, and Lisa Walker.

Table of Contents

List of Chapter 2 Tables: Study 1 Tables

List of Chapter 2 Supplementary Tables: Study 1 Supplementary Tables

List of Chapter 3 Tables: Study 2 Tables

List of Chapter 4 Tables

List of Chapter 5 Tables

Appendices

List of Acronyms Used in Thesis

AD: Alzheimer's Disease

aMCI: Amnestic Mild Cognitive Impairment

APOSTLE: Advised Protocol for OCT Study Terminology and Elements

CI: Cognitive Impairment

CRF: Cardiorespiratory Fitness

EF: Executive Function

EDSS: Expanded Disability Status Scale

FSS: Fatigue Severity Scale

GC: General Cognitive Function

GCIPL: Ganglion Cell and Inner Plexiform Layer

GCL: Ganglion Cell Layer

GM: Grey Matter

HADS: Hospital Anxiety and Depression Scale

HRQoL: Health-Related Quality of Life

I_{EF}: Insight of Executive Functions

I_{GC}: Insight of General Cognition

IPS: Information Processing Speed

IQ: Intelligence Quotient

LTPS: Leisure Time Physical Activity Score

MCI: Mild Cognitive Impairment

METs: Metabolic Equivalents

MRI: Magnetic Resonance Imaging

MS: Multiple Sclerosis; three subtypes discussed

- Relapsing Remitting Multiple Sclerosis (RRMS)
- Secondary Progressive Multiple Sclerosis (SPMS)
- Primary Progressive Multiple Sclerosis (PPMS)

MV: Macular Volume

NeuroQOL GC: Neuro-QOL item bank V 1.0 - applied cognition - general concerns (PRO_{GC} measure used in thesis)

NeuroQOL EF: Neuro-QOL item bank V 1.0 - applied cognition - executive function (PRO_{EF} measure used in thesis)

OCT: Optical Coherence Tomography

ON: Optic Neuritis

OSCAR-IB: Obvious, Signal Strength, Centred, Algorithm Failure, Retinal Pathology, Illumination, Beam Placement criteria for OCT quality control

PASAT: Paced Auditory Serial Addition Test

PPMS: Primary Progressive Multiple Sclerosis

pRNFL: Peripapillary Retinal Nerve Fiber Layer

PRO: Patient-Reported Outcome

PRO_{GC}: Patient-Reported Outcome of General Cognition

PRO_{EF}: Patient-Reported Outcome of Executive Function

PRO_{memory}: Patient-Reported Outcome of Memory

PRO_{IPS}: Patient-Reported Outcome of Information Processing Speed

QOL: Quality of Life

RNFL: Retinal Nerve Fiber Layer

RRMS: Relapsing-Remitting Multiple Sclerosis

SCD: Subjective Cognitive Decline

SPMS: Secondary Progressive Multiple Sclerosis

Stroop: The Stroop Colour Word Test, offers four scores

- W (word reading trial score)
- C (colour naming trial score)
- CW (incongruent colour-word, colour naming trial score)
- I (interference score – takes into account all trial scores. Ability to suppress habitual responding patterns to stimuli [written words] and instead generate a new, effortful response [naming of ink colour])

SDMT: Symbol Digit Modalities Test

$VO_{2\ peak}$: Peak volume of oxygen uptake across 20 second intervals during cardiopulmonary exercise testing (mlO_2 /kg/minute); a measure of CRF

WM: White Matter

Chapter 1: General Introduction

1.1 Multiple Sclerosis

Multiple sclerosis (MS) is a chronic, autoimmune, demyelinating, and neurodegenerative disease of the central nervous system that results in an array of motor, sensory, psychological, and cognitive symptoms (1). MS has a complex and poorly understood etiology involving synergistic genetic and environmental factors (e.g., prior Epstein-Barr virus infection, Vitamin D deficiency, obesity, smoking, etc; 2). Compared to other neurodegenerative diseases, MS is typically diagnosed at a young age (~30-40 years; 2) with three times as many females than males being affected by the disease (3). Canada has one of the highest prevalence rates of MS in the world, with 55-350/100,000 inhabitants having a diagnosis (4).

Individuals with MS are often differentiated by clinical course as relapsing-remitting (RRMS), secondary progressive (SPMS), or primary progressive MS (PPMS; 5). Approximately 80% of people with MS are initially diagnosed with RRMS (1). This presentation of the disease is typified by progression (i.e., accumulation of disability) through episodically increased disease activity and symptomatic emergence/worsening (i.e., relapses) followed by remissions of disease activity (6). Among those with RRMS, many go on to develop SPMS, which entails a progression that is usually unaccompanied by discernable relapses (6). Alternatively, ~20% of people with MS are initially diagnosed with PPMS (1), a course characterized by gradual disease progression typically lacking relapses from disease onset (6).

1.2 Cognitive Impairment in People with Multiple Sclerosis

1.2.1 The Significance of Cognitive Impairment for People with Multiple Sclerosis

Cognitive impairment (CI) affects 40-70% of people with MS throughout the disease course (7). CI has been observed within the first year of diagnosis (8) and even before MS

diagnosis in people with radiologically isolated and clinically isolated syndromes (9,10). Though cognitive deficits in MS are typically mild relative to other neuropsychological conditions affecting older adults, cognitive symptoms typically emerge in MS earlier in life and present barriers to one's family and career development (11,12).

The importance of preventing and managing CI is compounded by the fact that cognitive functioning is intimately connected to well-being in people with MS (13–18). That said, while CI in people with MS is associated with symptoms of anxiety and depression (15,19–22), CI remains a stronger predictor of reduced quality of life than low self-esteem and symptoms of anxiety and fatigue (13–18). The effects of mild CI in MS are well-documented with adverse impacts on income (23,24), workplace functioning and employment (24–28), driving performance (29,30), and ability to maintain social roles (24). Further, people with MS-related CI have worse treatment adherence and benefit less from cognitive rehabilitation relative to those without MS-related CI (31,32).

1.2.2 Characterization of Cognitive Impairment in Multiple Sclerosis

MS-related CI is typified by reduced information processing speed (IPS), which is usually the earliest and most commonly exhibited cognitive deficit in people with MS (33,34). IPS refers to the speed one can process and respond to a cognitively relevant stimulus (35). Although IPS is divided into perceptual, cognitive, and psychomotor components (35), it is usually measured as a single construct.

Impaired executive functions (EFs) are the second most common CI in people with MS (36). EFs are effortful, top-down cognitive processes that can be divided into three fundamental components: inhibitory control (including self-control [behavioral inhibition] and interference control [mental inhibition]), working memory, and cognitive flexibility (37). Higher-order EFs

like conceptual reasoning, problem-solving, and planning are believed to emerge from these elementary EFs (37). Inhibitory control is the ability to suppress impulses and conditioned responses and exert control over one's attention, behaviour, thoughts, and/or emotions to respond appropriately to stimuli within the context of a given task (37). Working memory refers to the ability to retain and mentally manipulate information after it is no longer perceptually present (37). Cognitive flexibility encapsulates one's ability to shift how they attend to, process, and respond to stimuli with respect to novel/changing task goals, demands, and opportunities (37,38).

1.2.3 Cognitive Reserve and Brain Reserve

Cognitive reserve conceptualizes resilience to neuropathology or aging in the form of maintained cognitive abilities (39,40). High reserve applies to persons with unexpectedly preserved cognition after a great degree of aging or cognitively relevant neurological insult. Greater cognitive reserve is associated with traits such as intelligence quotient (IQ), as well as modifiable modes of enrichment, such as formal education and recreation, social interaction, cognitively demanding vocations, and aerobic fitness (34,39,41–43). Cognitive reserve is likely mediated by the efficiency of cognitive networks – the minimal amount of activation required of a network to successfully perform a given task (39,40). Relatedly, cognitive reserve is thought to depend upon the capacity of cognitive networks – the maximum level of activation a network can generate to meet progressively complex task demands (39,40). The ability of networks to compensate in order to maintain task performance offers an additional mechanism of cognitive reserve (39,40). Compensation refers to the degree a network can maintain/enhance task performance by co-opting other neuronal tissue (39,40). In addition to these network properties, cognitive reserve may be subserved by one's potential to achieve successful task performance by

flexibly using different neural networks and/or using a given network in a more varied fashion to yield multifarious solutions (39,40).

Brain reserve exists as a conceptual counterpart to cognitive reserve (39,40,44). This model of resilience refers to inter-individual variability in structural properties – such as the number of neurons and their synapses – which engender protection against the clinical consequences of neuropathology (39,40,44). Greater brain reserve is posited to offer a buffer between neuropathology and functional deficit insofar as individuals retain the ability to capitalize on remaining neuronal tissue to meet the needs of a given function (39,40,44). That said, brain reserve is presumably a more static concept of resilience which is determined by less adaptable structural properties of the brain (39,40,44).

In connection to brain reserve, brain maintenance has been invoked as the decreased rate of aging and/or pathology in the brain as a consequence of genetics and environment (39,40,45). For example, in people with MS, evidence suggests that physical activity and exercise training offer facilitators of brain maintenance (46–50). Brain maintenance is typically measured longitudinally via the accumulation of pathology over time; however, maintenance can be measured residually, by comparison of the structural properties of an individual's brain to what would be demographically expected (i.e., what is typical of one’s age, sex, etc; 39,40).

The Clinico-Radiological Paradox (51) describes inter-individual variation in the extent of neurological dysfunction given similar degrees of radiologically measured neuropathology. Mechanisms of reserve offer some explanation of the cognitive facet of this phenomenon (52). Models of reserve (39,40,44) facilitate understanding of what otherwise remains unexplained – discrepancies between structural pathology and clinically measured function. Individual differences in susceptibility to CI prevent straightforward explanations of the pathophysiology of

MS-related CI insofar as a metric of pathology may have differential cognitive effects between individuals. One should thus keep in mind reserve while considering the neural correlates of CI.

1.3 Studying the Substrate of Cognitive Impairment in Multiple Sclerosis: Insights from Structural Imaging

1.3.1 A Radiological Description of Cognitive Impairment in Multiple Sclerosis

Structural magnetic resonance imaging (MRI) research on CI in MS conventionally concerns lesion load (i.e., the number and/or volume of focal areas of e.g., inflammation and neurodegeneration) and diffuse measures of neurodegeneration (i.e., atrophy; 43,53). In MS, CI has been associated with elevated cerebral lesion load (54–57), as well as the number and volume of white matter (WM), cortical, and deep gray matter (GM) lesions (57–59). Literature on the relative importance of WM, cortical, and subcortical GM lesions to CI is mixed (57), and the same can be said of GM and WM atrophy (57,58,60,61). That said, atrophy is a stronger correlate of CI than are lesions in people with MS (43,61,62). At any rate, these findings are rather intuitive. A more elusive and perhaps insightful question one can pursue is: in what anatomical structures is neuropathology most relevant to CI in MS? To this end, there exists a large body of literature. Indeed, atrophy of the thalamus, caudate, amygdala, pallidum, nucleus accumbens, putamen, hippocampus, and cerebral cortex are related to CI in MS (57,58,60,63,64).

A common observation has been that atrophy of highly interconnected structures is highly related to CI in MS. Damjanovic et al., (2017; 58) suggest that highly interconnected GM structures (e.g., thalamus) presenting important nodes in many cortical, striatal, limbic, brain stem, and cerebellar systems, are typically associated with CI, because they are integral to many forms of information processing and integrated cognition. This may make sense of the fact that there is not one cause of CI in MS; but rather, cognitive decline (especially in IPS and EF) is

strongly correlated with MS neuropathology in several brain regions (65). In fact, dysfunctional IPS and EF display more sensitivity to cerebral WM integrity than the standard measure of MS disability (e.g., the Expanded Disability Status Scale; EDSS; 66,67).

Despite providing numerous gold-standard metrics of MS pathology, MRI is not without its shortcomings relative to more accessible imaging biomarkers derived from retinal optical coherence tomography (OCT). Technologically speaking, OCT bests MRI in a number of domains, including ease and speed of operation, cost, accessibility, spatial resolution, and test-retest reliability (68–71). OCT can also be used to image people with contraindications to MRI such as an implanted pacemaker, baclofen pump, or claustrophobia (69,70).

1.3.2 Retinal Optical Coherence Tomography as a Neuroradiological Tool

Retinal pathology and changes in visual function have been documented to precede and/or co-occur with pathological changes throughout the brain and their clinical manifestations in a number of neurological diseases (72,73). OCT has therefore gained interest as an MS research/care tool. Spectral-domain OCT operates using near-infrared low-coherence interferometry (68). This reliance on near-infrared light implicates that OCT can only be used to image tissues accessible to light. Ergo, MRI is preferable to noninvasively image enclosed structures that are not exposed to light. Hence, OCT biomarkers of neuroaxonal damage and inflammation in the form of atrophy (i.e., thinning) and thickening of retinal structures, respectively (69,70,74,75), can be used to complement MRI to detect disease activity in clinically stable patients (70). Importantly, OCT biomarkers of neuroaxonal damage have been related to IPS, verbal fluency, visuospatial memory, and verbal memory in people with MS (70).

1.3.2.1 RNFL and GCIPL: Biomarkers of Neuroaxonal Damage

Retinal photoreceptors send visual information through the bipolar cell layer and subsequently toward the ganglion cell layer (GCL; 71). Ganglion cells transmit signals via axons to the optic nerve. These axons compose the retinal nerve fiber layer (RNFL). RNFL and GCL thinning in MS are interpreted as retinal axonal and neuronal atrophy due to retrograde degeneration from damage to the optic nerve, tracts, chiasm, thalamus, and radiations (69,71,74,76). Parisi et al. (1999; 77) first used OCT to quantify retinal atrophy in MS in the RNFL. Since then, thinning around the optic disc in the peripapillary retinal nerve fiber layer (pRNFL) has been a commonly used OCT biomarker in MS.

Macular volume (MV) has been used in place of the ganglion cell and inner plexiform layer (GCIPL) as a crude biomarker of neurodegeneration (69). Advancements in segmentation software have resulted in more widespread use of the GCIPL. The GCIPL has advantages over the pRNFL as a biomarker. First, compared to pRNFL thickness, GCIPL thickness is a stronger correlate of visual acuity in people with MS (78) and several metrics of brain atrophy (79). The structure's second advantage stems from the GCIPL being less affected by optic neuritis (ON; inflammation coupled with demyelination of the optic nerve; 80,81). Although there is often substantial functional recovery in people with MS, marked permanent atrophy following ON often remains (80,81). Because the GCIPL does not thicken during ON as does the pRNFL, GCIPL atrophy can be detected four weeks after ON, whereas pRNFL atrophy may go undetected for months (69,82,83).

1.4 Subjective Cognitive Impairment in People with Multiple Sclerosis

1.4.1 Cognitive Patient-Reported Outcomes in Multiple Sclerosis

Several expert neuropsychologists have indicated that clinics offering neuropsychological examination are too busy to frequently examine patients to detect subtle cognitive changes in people with MS (84). Standardized measurement tools of patient-reported cognition offer accessible options to inexpensively, quickly, and remotely inform of CI and to determine potential need for neuropsychological assessment. Assessing patient-reported cognition may also facilitate understanding of an individual's real-world function, as it has been expressed: “Often, standard [neurological] tools do not assess relevant information regarding day-to-day functioning, especially for patients with conditions characterized by chronic pain, cognitive deficiencies, fatigue or functional decline” (85; P1). As such, it has been argued that there remains a need in clinical practice to measure patient experiences of neurological functions (85).

Both patient-reported memory and general cognition have been observed to predict real-world functioning (e.g., employment status and reduction in work hours) beyond the effects of cognitive performance (86). These subjective, patient-centered measures of health-related variables are referred to as patient-reported outcomes (PROs; 87,88). Much like the complimentary role of OCT to MRI in MS radiology, cognitive PROs offer much potential in the realms of clinical and experimental neuropsychology as screening tools, and in some cases, as brief measures of cognition.

In addition to incorporating the patient experience, cognitive PROs have been argued to be the most practical early warning sign of cognitive decline in people with dementing diseases, such as HIV (89). This reasoning could be extended to people with MS. Indeed, cognitive PROs have been theorized to be more sensitive than performance-based screening measures (i.e., brief

cognitive tests/batteries) to initial cognitive decline in people with MS since they are rated relative to an individual's prior functioning (84,90). In contrast, one's baseline neuropsychological test performance is compared to normative data of demographically similar others. In turn, individuals of premorbid functioning greater than the 50th percentile of their demographic may report cognitive decline; but in the absence of premorbid data, their test performance can be interpreted as 'normal', even if they have had meaningful objective cognitive decline (e.g., >1.5 SD; 84).

The use of cognitive PROs to gauge cognitive decline, however, is not without challenges. Fatigue, depression, and cognitive status have been discussed as factors that potentially impact the responses of people with MS on cognitive PROs (91–94). Notably, cognitive PROs have been reported to be more strongly related to symptoms of depression and fatigue, and low self-esteem than to objective cognitive performance in people with MS (94–98).

1.4.2 On the Relationship between Cognitive Patient-Reported Outcomes and Cognitive Performance

Despite the degree to which cognitive PROs are related to putative confounds (i.e., symptoms of depression and fatigue), general cognitive concerns on PROs predict IPS and memory performance, independent of mood, disability, fatigue, and age in people with MS (99). Importantly, the strength of the relationship between cognitive PROs and objective cognitive performance might vary according to the cognitive functions assessed. For example, compared to other cognitive PROs, PROs of executive function (PRO_{EF}; e.g., Frontal Systems Behavior Scale [FrSBe]; the Dysexecutive Questionnaire [DEX]; 100,101) generally have the strongest relationships to cognitive performance in MS (92,102–104). Among people with MS, PRO_{EF} have been related to performance on non-executive tests of verbal learning, manual dexterity,

and IPS (92,102), and executive tests of planning, working memory, verbal fluency, and cognitive flexibility (92,102). PRO_{EF} are often more strongly correlated with multi-measure executive composite scores than with single executive/nonexecutive test scores in people with MS (92,103).

In contrast to PRO_{EF}, findings regarding memory PROs (PRO_{memory}) are more nuanced. For example, PRO_{memory}, have been found to be unrelated to IPS and specific EFs, such as planning, inhibition, and working memory in people with MS (97,105). Conversely, PRO_{memory} are strongly correlated with executive composite scores and initial trial learning on verbal memory tasks, but are minimally related to subsequent trial learning or delayed recall in people with MS (97,105–107). In comparison, general cognitive PROs (PRO_{GC}) have little to no association with IPS, memory, and batteries of GC performance (86,98,108,109), but are more strongly related to EFs (e.g., verbal fluency and working memory; 110).

MS literature on the relationship between cognitive PROs and cognitive performance is scant; however, some emergent patterns can be observed across study findings. First, compared to other objective cognitive outcomes, executive performance most strongly and reliably relates to cognitive PROs (e.g., PRO_{EF}, PRO_{memory}, and PRO_{GC}; 97,103,105,106,110). Second, compared to other cognitive PROs, PRO_{EF} most strongly and reliably relates to objective cognitive outcomes (92,102–104). Additional patterns can be observed across study findings concerning individuals with MS who lack 'insight' – herein, referring to one's awareness of their illness/impairment (111). Typically, large discrepancies between self-reported cognition and objective indicators of cognition (e.g., caregiver reports or cognitive test performance) are interpreted as low insight of MS-related cognitive decline (112). Individuals who lack such insight generally have lower cognitive performance than others with MS who maintain insight

(112–114). Furthermore, low insight in MS corresponds with especially low EF performance (112,113). Collectively, these findings might reflect a general importance of EFs for maintaining one's insight into their own cognitive status.

1.4.2.1 Gaps in Knowledge Concerning the Relationship between Patient-Reported Cognition and Objective Neuropsychological Outcomes

MS literature to date suggests that one's reporting of their EF – relative to other cognitive PROs – might offer the best indication of their objective cognitive performance (92,102–104). This finding highlights the potential utility of PRO_{EF} over PRO_{GC} for the screening of objective CI in people with MS. In the case that PRO_{EF} may uniquely inform of MS-related CI, it could also be the case that EF insight is a stronger correlate of objective neuropsychological outcomes than are other forms of cognitive insight. In clinical settings, where there may be an interest in screening persons for CI, reduced insight might offer another screening outcome if one uses cognitive PRO(s) in combination with a few brief cognitive tests. Research is lacking, however, on whether executive insight is a stronger correlate of objective neuropsychological outcomes than is general cognitive insight.

There is a dearth of MS research on insight to guide interpretations of discrepancies between patient-reported cognitive dysfunction and clinically observed cognitive test performance in persons with MS. It remains unknown to what degree "overestimations" of CI by people with MS are attributable to psychological confounds altering the accuracy of patient-reported cognition. Conversely, it remains unclear to what degree such overestimations reflect certain individuals being more sensitive than cognitive test scores to the subtle cognitive effects of MS. The Clinico-Radiological paradox (discussed in *Section 1.2.3*) is presumably due to inter-individual variability in how individuals are affected by neuropathology (e.g., cognitive reserve),

radiological measurement error of disease pathology, and the inability of clinical measures to fully detect functional changes resulting from neuropathology (51,52,115,116). This latter factor provides support for investigating potential linkages between radiological metrics of disease burden and patient-reported cognitive function.

Scant MS literature addresses the relationship between cognitive PROs and neuroradiological outcomes (e.g., 117) and none has investigated the association between insight and neuroradiological outcomes. Kletenik et al. (2019; 117) observed PRO_{GC} to be weakly associated with thalamic and cortical gray matter atrophy. However, cognitive PROs seemingly have domain-specific relationships to cognitive performance (*discussed in Section 1.4.2*); ergo, domain-specific investigation of their relationships to neuroradiological outcomes is appropriate.

Investigating the extent to which objective radiological outcomes relate to both cognitive PROs and insight could help to elucidate the utility of cognitive PROs experimentally/clinically as stand-alone measures and in combination with objective test performance. For example, if insight metrics are related to radiological outcomes, the use of cognitive PROs may be extended beyond isolated screening tools or surrogates of cognitive abilities to tools complementing objective neuropsychological assessment. This could, in turn, enhance our understanding of one's disease status and burden.

1.5 Aims of Chapter 2: How Patient-Reported Cognition and Insight Relate to Objective Neuropsychological Outcomes in People with Multiple Sclerosis

The aims of Study 1 were to address the degree to which cognitive PROs and/or insight are related to: 1) objectively measured cognitive performance; 2) objective neuroradiological outcomes (pRNFL and GCIPL atrophy); and 3) symptoms of depression and fatigue. Aim 1 was

addressed by hypotheses 1-2. Hypothesis 1 predicts which cognitive performance measures are more related to PRO_{EF} (EF > GC/IPS) and PRO_{GC}, (EF>GC/IPS):

1. PRO_{EF} and PRO_{GC} will more strongly correlate with objective EF performance (EF in general and interference control in particular) than GC or IPS performance in people with MS.

Hypothesis 2 concerns which cognitive PRO (PRO_{EF} > PRO_{GC}) is more associated with cognitive performance:

2. Objective cognitive performance (EF in general, interference control in particular, IPS, and GC) will more strongly correlate with PRO_{EF} than PRO_{GC} in people with MS.

Relative to Aim 2, hypotheses 3-4 were:

3. PRO_{EF} and PRO_{GC} (and respective insight: I_{EF} and I_{GC}) will positively correlate with pRNFL and GCIPL thickness in people with MS.
4. Retinal thickness (pRNFL and GCIPL) will more strongly correlate with PRO_{EF} than PRO_{GC} in people with MS.

As there were no a priori hypotheses concerning relationships between cognitive PROs/insight and symptoms of fatigue and depression, Aim 3 was addressed by exploratory correlations.

1.6 Beyond Correlates of Patient-Reported Cognition: What Can be Done to Preserve or Improve Subjective Cognitive Functioning in People with Multiple Sclerosis?

It remains largely unclear how the cognitive effects of MS should be effectively managed and/or treated. In the absence of reproducible and compelling evidence for the efficacy of pharmacological options for the management/treatment of MS-related CI (118), interest has accrued towards behavioral approaches (e.g., exercise training; 119). To inform the development

of trials for managing MS-related CI, recent research has focused on how exercise targets (i.e., components of physiological fitness) relate to cognitive performance in MS (119,120). In the interest of understanding how to mitigate the cognitive effects of MS – effects which objective cognitive metrics can be insensitive to (84,85,90) – Study 2 probed for evidence of potential protective effects associated with cardiorespiratory fitness (CRF), as a marker of physical activity and exercise, against patient-reported cognitive symptoms.

1.6.2 Towards a Comprehensive Understanding of the Role of Exercise in the Management of Cognitive Dysfunction in People with Multiple Sclerosis

Physical activity can be defined as "any bodily movement produced by contraction of skeletal muscles that [increases] energy expenditure over resting values" (121). Exercise refers to physical activity that is "planned, structured, repetitive and purposive in the sense that improvement or maintenance of [component(s)] of physical fitness is an objective" (121). Fitness can be defined as "a set of attributes or characteristics that describes one's ability to do or perform physical work" (122). Physical activity in daily life, aerobic exercise training, and cardiorespiratory fitness (CRF: e.g., $VO_{2\ peak}$) have been associated with protective effects against disease-related and aging-related neurocognitive changes in people with MS and aging populations (46,47,123–129).

Understanding relationships between cognitive function, features of exercise, and targeted exercise-induced physiological adaptations will be instrumental to developing exercise interventions for managing the cognitive effects of MS. Previous findings on the cognitive effects of exercise training in people with MS have been mixed. Sandroff et al., (2016; 120) systematically reviewed 9 studies on exercise training in people with MS and reported that 4/9

studies indicated positive effects of exercise training on cognitive functions, whereas 5/9 studies indicated no statistically significant effects.

In their review of MS studies on relationships between cognitive performance and physical activity, exercise training, and physical fitness, Sandroff et al., (2016; 120) noted that an important determinant of whether a study achieved statistical significance was whether it included cognition as a primary outcome (120). In the 9/26 studies in which cognitive ability was a secondary outcome, 7/9 reported null findings (120). In contrast, 15/17 of studies including cognitive functions as primary outcomes reported significant positive effects of exercise, fitness, and physical activity (120). Corroborating this pattern, a 2020 review of 13 papers on the cognitive effects of exercise training in people with MS reported that 8/8 studies that included cognition as a primary outcome reported statistically significant cognitive effects of exercise training (119).

Given that exercise is a form of physical activity, the development of behavioural interventions might be informed by research examining physical activity in relation to cognitive functioning in people with MS. Regarding physical activity, the previously discussed 2016 review indicated that 4/6 studies reported significant positive associations between cognitive performance and physical activity in daily life (120). Notably, the 2/6 studies that reported null findings were also the only to include cognitive functioning as a secondary outcome. Like physical activity, fitness is also intimately connected with exercise as it is, by definition, an intended outcome of exercise training (121). Sandroff et al., (2016; 120) also reviewed eight studies on the relationship between physiological fitness (CRF, body composition, muscular strength, balance) and cognitive performance in people with MS. Interestingly, cognitive performance was a primary outcome in all fitness studies, with 7/8 reporting significant positive

associations between fitness and cognitive performance in people with MS (120). Further, 6 of these fitness studies examined relationships between CRF and cognitive performance in people with MS, with 6/6 of these studies reporting significant associations, such that greater CRF was associated with faster IPS (120).

Prior research has been criticized for being inconsiderate of how CI (or a lack thereof) may determine the cognitive gains yielded by exercise intervention (119,120). Sandroff et al., (2016; 120) speculated that ceiling effects associated with intact cognitive function may underpin some of the non-significant associations documented between cognition and fitness, physical activity, and exercise in people with MS. In line with this, subsequent data in people with MS has indicated that CRF is strongly related to IPS, but only in those with IPS CI (130). Likewise, the relationship between daily physical activity and IPS has been found to be stronger in people with MS and IPS CI relative to those with MS of preserved IPS (131). Efforts to understand how CI determines the cognitive effects of exercise training indicate that CI facilitates cognitive improvements across the MS-related disability spectrum. One study (132) characterized the response heterogeneity in terms of cognition following multimodal exercise training in people with moderate-severe MS-related disability. Notably, 41% of participants exhibited clinically meaningful improvements in terms of IPS, with improvements typically coinciding with lower CRF and slower IPS at baseline (132). Similarly, another study reported that in an MS sample who uniformly had minimal ambulatory disability but met IPS CI criteria, lower baseline IPS was moderately associated with greater IPS improvements after aerobic exercise training (123).

Given that IPS CI is the most prevalent manifestation of CI in people with MS (36), much of the literature addressing the potential of exercise for the management and treatment of CI in people with MS has focused on IPS. While comparatively smaller, there does exist similar

literature for other areas of cognition affected by MS. One study reported non-significant relationships between CRF and GC, verbal fluency, verbal memory, and visuospatial memory, while simultaneously finding that only IPS was significantly related to CRF (133). In comparison, a study that exclusively involved people with MS with IPS and/or memory CI found that daily physical activity levels were related to IPS, but not memory performance (125).

Against this backdrop, experimental studies have been published addressing the effects of aerobic exercise training on memory performance in people with MS. One pilot study (n=11) reported that relative to controls with MS-related CI, people with MS-related CI who had undergone aerobic exercise training displayed moderate-large, non-statistically significant improvements in memory performance (50). Notably, this study also documented that people with MS who received exercise training demonstrated preserved hippocampal volume relative to controls (50). Similarly, a larger study (n=130) comparing the cognitive effects of two aerobic exercise interventions in people with MS reported that those receiving either intervention tended to exhibit gains in memory and IPS, with baseline CI predicting greater memory improvements (134).

With respect to the protective effects associated with physical activity, CRF, and aerobic exercise for EF, there is a dearth of literature compared to that concerning IPS and memory in people with MS. That said, data suggest a relationship exists between CRF and preserved interference/inhibitory control and cognitive flexibility, insofar as people with MS who have greater CRF have faster responses to test stimuli (135,136). Evidence additionally indicates that these effects are pronounced in people with MS who have IPS impairment and are nullified in people with preserved IPS (130).

1.7 Aims of Chapter 3: An Examination of the Protective Effects of Cardiorespiratory Fitness for Patient-Reported Cognitive Symptoms in People with Multiple Sclerosis

As it has been expressed elsewhere, conventional neurological tools fail to capture the entirety of affected persons' neurological symptoms (85). Accordingly, scientific inquiry into the management and prevention of CI as it is measured through the lens of the patient-reported cognitive function is lacking. Despite a body of literature indicating exercise, physical activity, and fitness may be fruitful approaches to managing and potentially rehabilitating objective CI in people with MS, there is a glaring gap concerning the effects of exercise and related targets on cognitive PROs.

While no research has examined the potential protective effects of CRF for cognitive PROs, studies have indicated a positive relationship between the frequency of physical activity and PROs of prospective and retrospective memory in people with MS (137). However, physical activity has been observed to be unrelated or weakly related to PRO_{GC} (137,138), except in people with MS who engage in moderate-high physical activity levels (139). Considering this and that no research has examined the relationship between PRO_{EF} and CRF, the proposed study aimed to address: 1) the degree to which cognitive PROs are associated with CRF. It was hypothesized that cognitive PROs would positively correlate with CRF in people with MS.

1.8 Summary

Cognitive PROs are promising screening tools and measures of real-world cognitive function. As has been argued elsewhere: “Often, standard [neurological] tools do not assess relevant information regarding day-to-day functioning” (85; P1). To better understand the extent to which persons with MS are affected by their disease or by a related intervention, patient experiences of neurological functioning are crucial to assess via PROs (85). This thesis aimed to

better understand: i) the neuropsychological utility and interpretation of cognitive PROs in MS; and ii) the potential protective effect on cognition associated with maintaining physiological fitness in MS. Study 1 characterized how certain features of patient-reported cognition correlate with objective neuropsychological outcomes and putative confounds (i.e., depression and fatigue) in people with MS. Study 2 assessed whether CRF is associated with cognitive PROs in people with MS.

Chapter 2: Study 1

Patient-Reported Cognitive Dysfunction Reflects Affected Objective Neuropsychological Outcomes in People with Multiple Sclerosis

Abstract

Interpreting patient-reported outcomes (PROs) of cognition requires an understanding of the nature in which cognitive PROs and insight (i.e., self-awareness of illness/impairment) relate to objective neuropsychological outcomes. Compared to PROs of general cognition (PRO_{GC}), PROs of executive function (PRO_{EF}) might more reliably correlate with cognitive performance in people with multiple sclerosis (MS). No MS research has examined relationships between PRO_{EF} and radiological outcomes. This study aimed to quantify the degree to which cognitive PROs and insight relate to: i) cognitive performance; ii) radiological biomarkers of neuroaxonal degeneration; and iii) putative confounds (i.e., depression and fatigue) in people with MS. Tests of information processing speed (IPS) and executive functioning (EF) assessed cognitive performance. Questionnaires measured PRO_{GC}, PRO_{EF}, fatigue, and depression. Discrepancy scores between cognitive performance and PROs operationalized insight. Optical coherence tomography (OCT) was used to measure ganglion cell-inner plexiform layer (GCIPL) and peripapillary retinal nerve fiber layer (pRNFL) thicknesses – biomarkers of neuroaxonal degeneration. Spearman's correlations were used to investigate relationships between primary outcomes in 7 people with MS and 9 controls. In the MS group, cognitive PROs correlated more strongly with the most affected objective outcomes relative to their less affected counterparts. In participants with MS, overestimation of cognitive dysfunction coincided with slow IPS, unimpaired EF, and GCIPL atrophy; however, putative confounds of cognitive PROs – depression and fatigue – were unrelated to insight. Preliminary findings support the use of cognitive PROs for screening/monitoring neuropsychological decrements in people with MS. Further research is needed to replicate and expand upon the present findings.

Introduction

Multiple sclerosis (MS) is a demyelinating, neurodegenerative, autoimmune disease of the central nervous system (CNS; 1). Approximately, 40-70% of people with MS exhibit cognitive impairment (CI; 2), most commonly in information processing speed (IPS), executive functioning (EF), and memory encoding (3). MS-related CI is associated with disruptions in indices of real-world functioning, such as workplace functioning and employment (4–8), driving performance (9,10), and maintenance of social roles (7). Detecting CI via neuropsychological assessment can facilitate disability-related supports (e.g., workplace accommodations) and elucidate needs for specific rehabilitative cognitive strategies (11).

Despite widespread use, conventional neuropsychological outcomes may fail to capture the full extent to which persons are affected by their disease (12,13). Patient-reported outcomes (PROs) of cognitive functioning offer promising options to feasibly inform of real-world dysfunction. Because cognitive PROs often index an individual's comparison between their current and prior functioning, cognitive PROs may further be useful in identifying early functional changes (13,14). In contrast, one's initial cognitive test performance is compared to normative data of demographically similar others. Sole reliance on cognitive test performance may thereby delay the detection of meaningful cognitive decline in individuals of higher premorbid functioning for their demographic (13).

Middelton et al., (2006; 15) speculated that people with MS may have inaccurate perceptions of their cognitive functioning; indeed, patient-reported general cognition (PRO_{GC}) has repeatedly been observed to be more related to depression and fatigue than general cognitive performance in MS (15–17). Conversely, PRO_{GC} in people with MS predicts IPS and memory performance, independent of mood and fatigue (18). Furthermore, PRO_{GC} and PRO of memory

function predict real-world functioning (e.g., employment status and reduction in work hours) beyond cognitive test performance in people with MS (19). That said, literature in aggregate suggests that PRO_{GC} (20), PRO_{memory} (21,22), and PROs of IPS (23) generally have small and unreliable correlations with cognitive performance in people with MS. In contrast, PROs of EF (PRO_{EF}) have reproducible, moderate-large associations with objective cognitive performance in people with MS (24–27).

Insight, herein referring to self-awareness of illness/deficit (28), is typically measured as the discrepancy between subjectively and objectively measured cognition (19,26,29–33). In MS literature, sufficiently large discrepancies between cognitive PROs and cognitive performance are often referred to as "overestimations" and "underestimations" of cognitive ability, impairment, or problems (19,26,31,32,34). Subjective cognitive decline (SCD) often precedes detectable CI in Alzheimer's disease (AD) and other dementing diseases, and coincides with elevated AD pathology (35,36). Within the SCD framework, SCD is characterized by self-perceived cognitive decrements despite the affected individual's semblance of demographically normal cognition in cognitive testing (14). In the context of the gradual accumulation of MS pathology, a similar stage plausibly exists within the continuum of MS-related cognitive decline. Diffuse CNS neuroaxonal degeneration in people with MS of demographically normal, albeit, subclinically affected cognition, would presumably be experienced as cognitive difficulty in daily life. This profile could be appraised by clinicians as overestimation of CI. Evidence that MS pathology is linked with overestimation of CI in people with MS may confer credence to certain experiences of dysfunction that remain undetected by neuropsychological assessment. Additionally, understanding which reports of CI more closely align with MS pathology could

help to identify which individuals are at risk of developing CI in the face of increasing disease pathology.

Keeping this background in mind, microvascular and/or neuroaxonal retinal pathologies precede the manifestation/detection of broader cerebral neuropathology in stroke, AD, primary CNS lymphoma, and MS (37). Accordingly, interest has burgeoned concerning the use of retinal optical coherence tomography (OCT) to complement magnetic resonance imaging (MRI) in monitoring disease activity and predicting disease outcomes in people with MS (38,39). OCT biomarkers of neuroaxonal damage are related to IPS, EF, verbal and visuospatial memory performance in people with MS (39). Such OCT biomarkers of neuroaxonal damage primarily include atrophy (i.e., thinning) of the macular ganglion cell and inner plexiform layer (GCIPL) and the peripapillary retinal nerve fiber layer (pRNFL; 38). MS-associated pRNFL and GCIPL thinning are largely due to retrograde degeneration from insult to the optic nerves, tracts, and chiasm, and less commonly transsynaptic retrograde degeneration from the visual cortices, optic radiations, and lateral geniculate nuclei (38). Importantly, these OCT biomarkers are related to radiological outcomes extending beyond the visual pathway in people with MS, including lesion load, whole brain and regional atrophy of the thalamus, corpus callosum, insula, cerebral cortex, basal ganglia, caudate nucleus, and cingulate cortex (40–46).

Elucidating relationships between cognitive PROs and potential confounds (e.g., depression, fatigue) and objective neuropsychological outcomes (e.g., cognitive performance and radiological metrics) is paramount to understanding how to use PROs to screen for neurocognitive changes in people with MS. Research addressing neuroradiological correlates of cognitive PROs is particularly scant. An MRI study documented PRO_{GC} to be associated with thalamic and cortical gray matter atrophy in people with MS (47). However, no MS literature has

investigated neuroradiological correlates of PRO_{EF} or insight. Ergo, the present study aimed to evaluate the extent to which cognitive PROs/insight are related to: i) cognitive performance; ii) radiological biomarkers of neuroaxonal degeneration; and iii) depression and fatigue in people with MS.

Method

Participants and Recruitment

The present research analyzed data from an ongoing study examining the neuroplastic effects of aerobic exercise paired with non-invasive brain stimulation in people with and without MS. The ongoing study was approved by the University of Ottawa Institutional Review Board (H-11-21-7484) and involved one baseline visit and three follow-up visits (acute sessions of exercise and/or non-invasive brain stimulation) each separated by approximately one week. Data presented herein were collected at the baseline visit. Recruitment occurred through postings and flyers disseminated in-person and online. Inclusion criteria for all participants were: 18-75 years old; able to communicate in English; asymptomatic as determined through Get Active Questionnaire (48) screening. Participants with MS were also required to have a(n): 3.0-7.0 Expanded Disability Status Scale (EDSS; 49) score; self-reported MS diagnosis, no relapses within the last 30 days, stable disease-modifying therapy treatment for the past six months. Individuals were excluded if they were pregnant or had moderate-severe CI (2 or 3) on the self-reported EDSS cognitive score (50).

Procedure

Participants were asked to refrain from caffeine, alcohol, tobacco, and exercise for 12 hours before their baseline visit. Participants underwent a fixed order of cognitive, EDSS (49),

and OCT examinations. Participants were given paper-based, English questionnaires and instructed to return them completed at their following visit.

Outcome Measures

Cognitive Performance

Cognitive tests were administered in the following order: oral Symbol Digit Modalities Test (SDMT; 51), Stroop Colour-Word Test (Stroop; 52), and Paced Auditory Serial Addition Test (PASAT 3"; 53). T-scores were produced using population norms (52,54). Discrete norms for the PASAT 3" and SDMT were developed with people 18-65 years old (54); participants 51-75 years old were scored using 51-65 age group norms. The PASAT 3-second version (53) was used to measure working memory. The Stroop interference score (Stroop-I; 52) measured interference control.

An EF composite was calculated as the mean of Stroop-I and PASAT 3" T-scores. Similarly to Hancock et al., (2022; 3), the SDMT (51) and word reading speed (Stroop-W; 52) measured IPS. An IPS composite was calculated as the mean of SDMT and Stroop-W T-scores. A general cognition (GC) composite was calculated as the mean of the IPS and EF composites (similar GC used elsewhere; 55). Greater scores on cognitive tests/composites reflect better cognitive performance.

Patient-Reported Cognition

The Quality of Life in Neurological Disorders (Neuro-QOL) V 1.0-applied cognition-general concerns (GC) and V 1.0-applied cognition-executive function (EF) short forms (56,57) were used to measure PRO_{GC} and PRO_{EF}, respectively. The 8-item NeuroQOL GC assesses general difficulties in cognition, whereas the 8-item NeuroQOL EF measures difficulties regarding everyday applications of EF. Items are answered on a 5-point scale ranging between 1

(Very often/several times a day/Cannot do) to 5 (*Never/None*). Greater scores reflect less cognitive difficulties. T-scores were generated using Neuro-QOL norms (58).

Insight

Discrepancy scores between cognitive composite and cognitive PRO T-scores provided an index of insight (similarly to 19,26; Table 2.1). Participants were categorized as "underestimators" and "overestimators" of CI if their discrepancy scores were less than or equal to and greater than or equal to the 25^{th} and 75^{th} percentile, respectively, of controls' discrepancy scores (26). The remaining participants were deemed "accurate" estimators of CI. More positive discrepancy scores reflect cognitive PROs indicating greater dysfunction in daily life than was detected via cognitive tests (i.e., overestimation of CI).

Retinal Morphology

Retinal biomarkers were measured without pupil dilation, by one operator, using a spectral-domain OCT apparatus (Heidelberg Spectralis HRA+ OCT2, Heidelberg Engineering, Heidelberg, Germany) and processing software (Heidelberg Eye Explorer 1.10, NSITE analytics 6.7). Multiple scans were taken per eye to ensure scans of sufficient quality. Optic disc-centred 12° ring scans (ART: 11 frames) measured pRNFL thickness. Fovea-centered 20° × 20° macular volume scans (512 A-scans, 49 B-scans, horizontal alignment, ART: 16 frames) measured GCIPL thickness as the mean thickness of the four quadrants of the 3mm ring. Image quality was assessed by an evaluator using Obvious, Signal Strength, Centred, Algorithm, Retinal Pathology, Illumination, Beam Placement (OSCAR-IB) criteria (59). OSCAR-IB (59) pathologies were queried via the above OCT scans and self-reported health history using the Self-Administered Comorbidities Questionnaire (60) and an internal eye health questionnaire. Because of the effect optic neuritis (ON) has on pRNFL and GCIPL thinning (61), eyes were also excluded if a

participant reported previous ON or if there was suspected previous ON per inter-retinal asymmetry thresholds (62). All pRNFL and GCIPL measurements from the included scans were averaged to obtain mean thicknesses of each structure in each participant's eye. Segmentation was semi-automated with manual correction of errors. Methodology and results are reported per the Advised Protocol for OCT Study Terminology and Elements (APOSTEL) guidelines (63). In accordance with the APOSTEL guidelines (63), reasons for excluding OCT scans can be found in Supplementary Table 2.1.

Fatigue and Depression

The Fatigue Severity Scale (FSS; 64) was used to measure fatigue severity over the past week via nine items ranging from 1 (*strongly disagree*) to 7 (*strongly agree*). The Hospital Anxiety and Depression Scale (HADS; 65) was used to measure depressive symptoms over the past two weeks. The HADS depression subscale consists of seven items each scored between 0 *(Not at all)* and 3 (*Most of the time*). Greater FSS and HADS scores represent higher severity of fatigue and depressive symptoms, respectively.

Neurological Disability

EDSS (49) score was determined through neurological examination to characterize disability level. Total scores range between 0 (*normal neurological function*) and 10 (*death due to MS*).

Demographics

Intake questionnaires measured demographic and clinical characteristics. Although education was measured ordinally herein, education level was converted per Supplementary Table 2.2 in calculating Stroop T-scores using Stroop norms (52).

Data Analysis

Analyses were conducted using IBM SPSS Statistics Version 29 (Armonk, NY). Preliminary Spearman's correlations were used to test potential demographic, clinical, and symptomatic covariates of retinal biomarkers, cognitive PROs, cognitive performance, and insight. Because potential covariates examined were not correlated to outcomes at the $p<0.05$ (two-tailed) level, none were controlled for in subsequent analyses. Relationships between cognitive PROs and: a) cognitive performance; b) radiological biomarkers; and c) symptoms of depression and fatigue were examined using Spearman's *rho* correlation coefficients. The magnitude of correlations were expressed as *rho* coefficient effect sizes (i.e., small≥0.10, moderate≥0.30, large≥0.50; 66). To facilitate the interpretation of correlations between cognitive PROs/insight and study outcomes, participants with MS were rank-ordered in a table according to their level of patient-reported cognitive function. Differences between participants with MS and controls in sample characteristics and primary outcomes were examined based on Cohen's *d* effect sizes (i.e., small≥0.2, moderate≥0.5, large≥0.8; 66), and independent sample t-tests. Statistical tests were considered statistically significant if $p<0.05$ (two-tailed).

Results

Sample Characteristics

Demographic and clinical descriptive statistics for controls (n=9) and participants with MS (n=7) are reported in Table 2.2. There was a large (d=0.81), non-statistically significant age difference between controls (M=40.75, SD=17.70) and participants with MS (M=53.75, SD=13.24). Few controls were female (33%), whereas the MS group was largely female (71%). Concerning the racial distribution, 22% of controls and 100% of the MS group were reportedly Caucasian. The sample was highly educated with 88% of participants having at least a bachelor's

degree. The MS group was mostly of a progressive disease course (71%), had a mild-moderate level of EDSS disability (Median=3.50, IQR=1.00), and had a mean disease duration of 9.33 years (SD=9.20).

Neuropsychological descriptive statistics are reported in Table 2.3. Cognitive performance was described in raw scores and T-scores; however, correlations and t-tests (discussed below) used T-scores. The MS group generally exhibited lower cognitive metrics than controls. These differences were mostly small-to-moderate in magnitude, but not statistically significant: PRO_{GC} (*d*=-0.38), PRO_{EF} (*d*=0.12), GC insight (I_{GC}; *d*=-0.07), EF insight (I_{EF}; *d*=-0.31), PASAT 3" (*d*=-0.28), Stroop-I (*d*=-0.37), EF (*d*=-0.46), Stroop-W (*d*=-0.57), SDMT (*d*=-0.60), GC (*d*=-0.86), and IPS (*d*=-0.93). The MS group also had large reductions in pRNFL (*d*=-0.81, *p*=0.08) and GCIPL (*d*=-1.63, *p*<0.01) thicknesses, and small-large elevations in symptoms of depression (*d*=0.32, *p*=0.54) and fatigue (*d*=1.65, *p* <0.01) relative to controls.

Overestimation and Underestimation of Cognitive Impairment in the MS Sample

Within the MS group, two participants surpassed thresholds of CI (-1.5 SD, i.e., <35 T; 41) with IPS being the only domain detectably impaired (Table 2.4). Notably, both participants with IPS CI were classified as "overestimators" of EF CI and one was further classified as having overestimated GC CI. Three participants with MS were classified as overestimating EF CI with two of these three participants also overestimating GC CI. Two and four participants with MS were classified as underestimating GC CI and EF CI, respectively; however, none were detectably impaired.

Participants with MS who overestimated EF CI (n=3) displayed intact EF performance with T-scores in the range of 53-61 (Table 2.4). This was in conjunction with slow IPS (T-scores in the range of 31-40) relative to all other participants with MS (T-scores in the range of 40-48).

In line with this, participants with MS that overestimated EF CI (n=3) displayed signs of more pronounced neurodegeneration as their GCIPL thickness ranged from 70-88μm, whereas the GCIPL thickness of all other participants with MS ranged from 87-101μm.

Correlations Between Cognitive PROs and Cognitive Performance

Correlations between cognitive PROs and cognitive performance are reported in Table 2.5. In participants with MS, the correlation coefficients between PRO_{EF} and cognitive performance occurred in a somewhat gradient fashion based on Cohen's *d* effect sizes. Namely, less affected cognitive outcomes (Cohen's *d* difference=[-0.28] – [-0.57]) were weaker correlates of PRO_{EF} (PASAT 3", Stroop-I, EF, Stroop-W [$rho \leq 0.20$, $p \geq 0.67$]) than more affected outcomes (Cohen's *d* difference=[-0.60] – [-0.93]): SDMT (*rho*=0.76, $p<0.05$), GC (*rho*=0.76, $p<0.05$), IPS (*rho*=0.70, $p=0.08$). The correlation coefficients between PRO_{GC} and cognitive performance in the MS sample were small-large, but not statistically significant, and occurred less consistently in the aforementioned gradient pattern: PASAT 3" (*rho*=-0.14), Stroop-I (*rho*=-0.67), EF (*rho*=-0.54), Stroop-W (*rho*=0.61), SDMT (*rho*=0.14), GC (*rho*=0.54), IPS (*rho*= 0.68).

Unlike in the MS group, PRO_{EF} correlated with executive performance in controls, specifically, Stroop-I (*rho*=0.76, $p=0.02$) and the EF composite (*rho*=0.72, $p=0.03$), but not the PASAT 3" (*rho*=0.23, $p=0.55$). Small-moderate, but not statistically significant correlations were observed between PRO_{EF} and other cognitive performance outcomes in controls: Stroop-W (*rho*=-0.30), SDMT (*rho*=0.41), GC (*rho*=0.35), IPS (*rho*=0.17). Small-large, but not statistically significant correlations were observed between PRO_{GC} and cognitive performance in controls: PASAT 3" (*rho*=0.14), Stroop-I (*rho*=0.26), EF (*rho*=0.47) Stroop-W (*rho*=-0.50), SDMT (*rho*=0.48), GC (*rho*=0.27), IPS (*rho*=0.16).

Correlations Between Cognitive PROs, Insight, and Retinal Biomarkers

Correlations between cognitive PROs, insight, and retinal biomarkers are reported in Table 2.6. In participants with MS, PRO_{EF} displayed moderate-large, non-significant correlations with pRNFL (*rho*=0.46, *p*=0.36) and GCIPL (*rho*=0.64, *p*=0.17) thicknesses. Likewise, PRO_{GC} exhibited a larger correlation with the more affected biomarker, GCIPL thickness (*rho*=0.60, *p*=0.21), than with pRNFL thickness (*rho*=-0.12 *p*=0.83). Congruently, EF insight (I_{EF}) demonstrated a larger correlation with GCIPL (*rho*=-0.71, *p*=0.11) than pRNFL (*rho*=-0.52, *p*=0.29) thickness, and GC insight (I_{GC}) more strongly correlated with GCIPL (*rho*=-0.60, *p*=0.21) than pRNFL (*rho*=0.12, *p*=0.83) thickness. Table 2.4 displays that positive coefficients between cognitive PROs and retinal biomarkers reflect lower patient-reported cognitive functioning coinciding with greater neuroaxonal degeneration, whereas negative coefficients between insight and biomarkers reflect CI overestimation occurring in parallel with greater neurodegeneration, albeit not at the level of statistical significance.

Correlations observed in controls between pRNFL thickness and cognitive PROs/insight were not statistically significant, and variable in effect size (negligible-large): PRO_{EF} (*rho*=-0.07), PRO_{GC} (*rho*=0.20), I_{EF} (*rho*=0.50), I_{GC} (*rho*=0.25). Correlations observed in controls between GCIPL thickness and cognitive PROs/insight were not statistically significant, and negligible-small in effect size: PRO_{EF} (*rho*=0.12), PRO_{GC} (*rho*=0.21), I_{EF} (*rho*=0.26), I_{GC} (*rho*=0.02).

Correlations Between Cognitive PROs and Symptoms of Depression and Fatigue

In participants with MS, there were negligible-moderate, not statistically significant correlations between depressive symptoms and PRO_{EF} (*rho*=-0.02, *p*=0.97), PRO_{GC} (*rho*=0.18; *p*=0.70), I_{EF} (*rho*=-0.31, *p*=0.50) and I_{GC} (*rho*=-0.18, *p*=0.70). In controls, moderate-to-large

correlation coefficients were observed between depressive symptoms and PRO_{EF} (*rho*=-0.42, *p*= 0.26), PRO_{GC} (*rho*=-0.65, *p*=0.06), I_{EF} (*rho*=0.74, *p*=0.02), and I_{GC} (*rho*=0.87; *p*=0.01), such that, as depression increased, controls were more likely to overestimate CI.

In participants with MS, there were moderate-large, non-statistically significant correlations between fatigue and PRO_{EF} (*rho*=-0.74, *p*=0.06), I_{EF} (*rho*=0.46, *p*=0.29), PRO_{GC} (*rho*=-0.36; *p*=0.43), and I_{GC} (*rho*=0.36, *p*=0.43). In controls, fatigue was inversely correlated with PRO_{EF} and PRO_{GC} (both *rho*<-0.70, *p*=0.02), such that, more fatigue coincided with lower patient-reported cognitive function. Fatigue additionally demonstrated large, non-statistically significant correlations with I_{EF} (*rho*=0.63, *p*=0.07) and I_{GC} (*rho*=0.58, *p*=0.10) in controls.

Discussion

Among participants with MS, PRO_{EF} more strongly correlated with affected cognitive (SDMT, GC, IPS) and radiological (GCIPL) outcomes than their less affected cognitive (PASAT 3", Stroop-W, EF, Stroop-I) and radiological (pRNFL) counterparts. This pattern of coefficients was also maintained in the correlations between insight (I_{EF} and I_{GC}) and pRNFL and GCIPL thickness in the MS group. The pattern of correlation coefficients observed between PRO_{GC} and objective neuropsychological outcomes (cognitive performance and radiological metrics) in the MS group less consistently followed this less-more-affected gradient. In controls, cognitive PROs/insight did not correlate with objective neuropsychological outcomes according to the gradient defined by the pattern of less-more affected outcomes in the MS group. This might suggest that the gradient of correlations observed in the MS group is potentially due to cognitive PROs being sensitive to affected objective neuropsychological outcomes in MS, rather than this pattern existing irrespective of MS-related cognitive decline.

Patient-Reported Cognition in Relation to Objective Neuropsychological Outcomes

One can reasonably assume that the GCIPL atrophy and the consistent, non-statistically significant reductions in cognitive performance T-scores in people with MS relative to controls largely reflect acquired neurological features attributable to MS pathology. Taken together with the relationships between PRO_{EF} and the most affected objective neuropsychological outcomes in the MS group, this pattern of evidence supports that PRO_{EF} in people with MS reflects the neuropsychological changes they have undergone. Extrapolating from this conclusion may help elucidate why PRO_{EF} was unrelated to executive performance in the MS group. The large, statistically significant correlations between PRO_{EF} and executive performance in controls support the validity of using PRO_{EF} to probe EF in the general population. However, the typical relationship between PRO_{EF} and EF performance might become nullified in cognitively affected MS samples with minimal EF decline – if in MS, PRO_{EF} reflects affected cognitive domains (e.g., IPS) rather than EF specifically.

In the current study, overestimation of GC CI and EF CI in participants with MS was characterized by preserved EF and apparently reduced IPS. Ergo, the concept 'overestimation of CI' in the context of the present study should be interpreted carefully as participants with MS who overestimated dysfunction could be construed as experiencing dysfunction in daily life that plausibly resulted from IPS decrements. Consequently, this finding may call into question the domain specificity of PRO_{EF}. Taken together with the statistically significant relationships observed between PRO_{EF} and cognitive performance (GC and SDMT), study findings provide preliminary support that PRO_{EF} may be a sensitive, non-EF-specific screening metric for MS cognitive dysfunction.

Because in the MS sample the strongest objective correlates of cognitive PROs were the most affected objective outcomes, preliminary findings support the validity of using cognitive PROs to screen/monitor people with MS for neuropsychological decrements. As the more-less affected gradient pattern of correlations was slightly more consistent for PRO_{EF} than PRO_{GC}, findings might support the superiority of PRO_{EF} as a neuropsychological screening tool in people with MS. Although 5/7 associations between PRO_{GC} and cognitive performance in the MS sample were large, 2/5 of these coefficients were negative, as higher executive abilities coincided with greater patient-reported GC dysfunction. These inverse associations highlight that patient-reported GC dysfunction in MS may not reflect GC per se. Rather, patient-reported GC dysfunction might specifically reflect non-executive decline while simultaneously indicating sufficient executive processes underpinning insight.

The SCD framework assumes that pathological involvement of cognitive networks may produce functional decrements that are not necessarily detectable by cognitive testing (14). Accordingly, the current study examined correlations between cognitive PROs, insight, and biomarkers of neuroaxonal degeneration. PRO_{EF}, PRO_{GC}, I_{EF}, and I_{GC} exhibited stronger correlations with the more affected biomarker (GCIPL) than with the less affected biomarker (pRNFL) in participants with MS. Moreover, participants with MS classified as overestimating EF/GC CI, had some of the most pronounced atrophy in the more affected biomarker (GCIPL). Taken together, our preliminary findings provide some indication that neuropsychological assessment may be insensitive to certain cognitive symptoms for which there is evidence of a neuropathological basis.

Fatigue: A Confound of Patient-Reported Cognition or a Symptom of Cognitive Decline in MS?

The observation that PRO_{GC} can more strongly correlate with fatigue and depression than with GC (15–17) has been used to argue that these symptoms may distort the accuracy of patient-reported cognition in people with MS (15). In the present study, cognitive PROs were unrelated to depression, whereas only PRO_{EF} exhibited a large, non-statistically significant correlation with fatigue in participants with MS. This accords with findings that compared to depression, fatigue is more related to cognitive PROs in people with MS (16,68).

Importantly, discrepancies between cognitive PROs and performance were unrelated to depression and fatigue in the MS sample and therefore did not appear to act as confounds of cognitive PROs. Findings thereby diverge from the documented relationship between fatigue and overestimation of GC CI in people with MS (32). Conversely, in controls, both insight metrics displayed large, non-statistically significant correlations with fatigue and large, significant correlations with depressive symptoms. Presumably, the MS sample was insufficiently powered to detect a relationship between insight and fatigue at the level of statistical significance. That being said, fatigue could alternatively be viewed as a potential symptom of neurocognitive decline in people with MS. Indeed, neuropathological cognitive fatigue is thought to result from disease involvement of a cognitive effort-reward processing network constituted by structures (e.g., dorsolateral prefrontal cortex, ventromedial prefrontal cortex, anterior cingulate cortex, striatum) that directly subserve cogitation and/or mediate its motivation (69–73).

Limitations

The non-experimental nature of this analysis prevents causal conclusions regarding study findings. The present analyses are of a small sample and findings need to be replicated in larger,

more diverse samples. Because 100% of the participants with MS were Caucasian, English-speaking, highly educated, and resided in an industrialized nation (Canada), findings might not generalize to people of different racial, ethnic, linguistic, socioeconomic, and cultural identities. Participant groups also differed substantially in their ethnic, racial, sex, and age composition which may limit the validity of between-group comparisons.

Participants were self-selected for subjectively deeming themselves unaffected by moderate-severe CI; in turn, this may limit our ability to extrapolate findings to people with MS who "accurately" estimate or "overestimate" having moderate-severe CI. Additionally, none of the participants with MS classified as underestimators of CI were detected to have CI. Study results should thus be considered reflective of an MS sample containing accurate and overestimators of CI, but no true underestimators of CI, rather, overestimators of cognitive ability.

This study had limitations pertaining to its measurement of primary outcomes. The GC composite would have better captured CI if there was a learning and memory component as this is the third most frequently impaired cognitive domain in MS (3). Moreover, the GC and EF composites could have better captured dysfunction via a more comprehensive assessment of executive abilities. Additionally, the pRNFL and GCIPL are, at best, proxies of structural disease burden in MS (40–46). This study's findings need to be elaborated with more direct biomarkers of global and regional, cognitively relevant, neuropathology.

Conclusion

Preliminary findings provide evidence for the sensitivity of cognitive PROs to the neurocognitive decrements experienced by people with MS. Findings indicate that PRO_{EF} correlates most strongly with affected neuropsychological domains in people with MS rather

than EF per se. Clinically, individuals with MS who report symptoms generally indicative of executive dysfunction ought to be assessed for CI more broadly than EF.

These initial findings indicate that the overestimation of CI may be partially attributable to IPS deficits in conjunction with intact EF. Importantly, discrepancies between cognitive PROs and cognitive performance (i.e., insight) were unrelated to putative confounds (depression and fatigue; 15,32) of cognitive PROs in participants with MS. Taken together, study results support assessing cognitive PROs to screen/monitor individuals with MS for neurocognitive decrements.

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Table 2.1 Summary of Cognitive Outcomes

Cognitive Domain	Objective Performance	Patient-Reported Outcomes (PROs)	Insight (I)
Executive Functions	EF=[(Stroop-I) + (PASAT 3")]/2	PRO_{EF}=Neuro-QOL EF	I_{EF}=[(EF) – (PRO_{EF})]
Processing Speed	IPS=[(SDMT) + (Stroop-W)]/2		
General	GC=[(IPS)+(EF)]/2	PRO_{GC}=Neuro-QOL GC	I_{GC}=[(GC) – (PRO_{GC})]
Insight Groups			UE CI=I ≤ 25th%ile OE CI=I ≥ 75th%ile

Note. EF=Executive Composite, PASAT 3"=Paced Auditory Serial Addition Test (3-second version), GC=General Cognitive Composite, IPS=Information Processing Speed Composite, SDMT=Symbol Digit Modalities Test, Stroop-W=Stroop Color Word Test Word Reading Trial score, Stroop-I=Stroop Color Word Test Colour Word interference control score, PRO_{EF}=Patient-Reported Executive Function, Neuro-QOL EF=Neuro-QOL item bank V 1.0-applied cognition-executive function. PRO_{GC}=Patient-Reported General Cognitive Symptoms, Neuro-QOL GC=Neuro-QOL item bank V 1.0-applied cognition-general concerns, I=Insight, UE=Underestimation, OE=Overestimation, CI=Cognitive Impairment.

Note. Raw cognitive metrics from the Stroop, PASAT 3", and SDMT, as well as PROs used in the above calculations, were converted into T-scores using normative data (145, 147, 151).

Table 2.2 Demographics and Clinical Characteristics

Sample Characteristic	Entire Sample (N=16)		MS (N=7)		Control (N=9)	
	Mean	SD	Mean	SD	Mean	SD
Age	45.95	16.97	53.75	13.24	40.75	17.70
	N	%	N	%	N	%
Sex (Female)	8	50	5	71	3	33
Race						
	N	%	N	%	N	%
Caucasian	9	56	7	100	2	22
African	2	13	0	0	2	22
Latino	1	7	0	0	1	11
Asian	1	7	0	0	1	11
Indigenous	1	7	0	0	1	11
Other	1	7	0	0	1	11
Unknown	1	7	0	0	1	11
Education						
	N	%	N	%	N	%
High School Diploma/Equivalent	1	6	0	0	1	11
College Diploma/ Equivalent	1	6	0	0	1	11
University Bachelor/Equivalent	4	25	4	57	0	0
University Masters Degree/Equivalent	7	44	2	29	5	56
University PhD/Equivalent	3	19	1	14	2	22
Clinical Characteristics						

Sample Characteristic	Entire Sample (N=16)		MS (N=7)		Control (N=9)	
	MDN	IQR	MDN	IQR	MDN	IQR
EDSS	-	-	3.50	1.00	-	-
	Mean	SD	Mean	SD	Mean	SD
Disease Duration (yrs)			9.33	9.20		
Clinical course	N	%	N	%	N	%
RRMS			2	29		
SPMS			1	14		
PPMS			4	57		

Note. EDSS=Expanded Disability Status Scale, RRMS=multiple sclerosis relapsing remitting subtype, SPMS=multiple sclerosis secondary progressive subtype, PPMS=multiple sclerosis primary progressive subtype, MDN=median, SD=standard deviation, IQR=interquartile range, N=sample size, %=percentage of participants.

Table 2.3 Neuropsychological, Radiological, and Symptomatic Outcomes in People with MS and Controls

Neuropsychological Outcome	MS (N=7)		Control (N=9)		*d*	*p*
	Mean	SD	Mean	SD		
Raw SDMT	53.16	7.57	63.83	13.65		
SDMT, T-score	44.70	8.09	51.30	12.53	-0.60	0.21
Raw PASAT 3”	50.75	5.97	52.08	5.85		
PASAT 3”, T-score	53.24	5.47	54.98	6.78	-0.28	0.55
Raw Stroop-W	93.75	14.62	100.75	13.55		
Stroop-W, T-score	37.29	11.13	43.01	9.50	-0.57	0.25
Stroop-I, T-score	56.75	7.38	59.17	5.98	-0.37	0.43
IPS	40.83	6.43	47.15	7.02	-0.93	0.07
EF	54.99	4.71	57.07	4.38	-0.46	0.33
GC	48.34	3.09	52.11	4.93	-0.86	0.09
PRO_{EF}, T-score	44.31	10.31	43.09	9.66	0.12	0.81
PRO_{GC}, T-score	40.53	11.19	44.44	9.72	-0.38	0.47
I_{EF}	11.54	11.13	14.53	8.21	-0.31	0.56
I_{GC}	7.81	10.91	8.56	10.54	-0.07	0.89
			Retinal Radiological Biomarkers			
pRNFL Thickness (μm)	93.75	6.45	100.23	8.88	-0.81	0.08
GCIPL Thickness (μm)	91.92	5.84	100.23	4.64	-1.63	<0.05
			Symptomatic Outcomes			
HADS	7.29	5.22	5.67	5.08	0.32	0.54
FSS	5.27	1.80	2.63	1.43	1.65	<0.05

Note. EF=executive composite, PASAT 3"=Paced Auditory Serial Addition Test 3", GC=general cognitive composite, IPS=information processing speed composite, SDMT=Symbol Digit Modalities Test, Stroop-W=Stroop Color Word Test Word Reading Trial score, Stroop-I=Stroop Color Word Test Color Word Interference Control Score, PRO_{EF}=patient-reported executive function, PRO_{GC}=patient-reported general cognitive symptoms, pRNFL=peripapillary retinal nerve fibre layer, GCIPL=ganglion cell and inner plexiform layer I=insight, HADS=Hospital Anxiety and Depression Scale (depression subscale), FSS=Fatigue Severity Scale, SD=standard deviation, N=sample size, *p*=two-tailed significance of independent sample *t*-test, *d*=Cohen's *d* effect size.

Note. I_{EF} and I_{GC} reflect discrepancies between T-scores (additional details in Table 2.1).

Table 2.4 Rank-Ordering Participants with MS Low-High [1-7] PRO_{EF}, PRO_{GC}, Cognitive Performance, and GCIPL Thickness

PRO_{EF} | PRO_{GC}	EF	IPS	GC	GCIPL (μm)
[1] 33^{OE} | [2] 30^{OE}	[2] 53	[3] 40	[2] 46	[3] 88
[2] 35^{OE} | [3] 34^{acc}	[5] 59	[2] 35*	[4] 47	[4] 88
[3] 37^{OE} | [1] 28^{OE}	[7] 61	[1] 31*	[1] 46	[1] 70^{1}
[4] 45^{UE} | [7] 59^{UE}	[1] 49	[5] 45	[3] 47	[5] 91
[5] 46^{UE} | [4] 40^{acc}	[4] 56	[6] 48	[6] 52	[2] 87
[6,7] 58^{UE} | [6] 48^{UE}	[3] 55	[4] 40	[5] 47	[6] 98
[6,7] 58^{UE} | [5] 45^{acc}	[6] 60	[7] 48	[7] 54	[7] 101

Note. PRO_{EF}=patient-reported executive function, PRO_{GC}=patient-reported general cognition EF=executive function composite, GC=general cognitive composite, IPS=information processing speed composite, GCIPL=ganglion cell and inner plexiform layer, UE=underestimate impairment, OE=overestimate impairment, acc=accurately estimate impairment.

Note. PRO_{EF}, PRO_{GC}, EF, IPS, and GC are reported in T-scores.

Note. *Indicates score met a commonly used threshold of CI (-1.5 SD; 41).

Note. [1] Indicates both eyes were excluded from statistical analyses due to non-MS retinal pathology.

Table 2.5 Spearman's Correlation Coefficients Between Cognitive PROs and Cognitive Performance

Neuropsychological Outcome	MS (N=7)				Control (N=9)			
Cognitive PRO	PRO_{EF}		PRO_{GC}		PRO_{EF}		PRO_{GC}	
	rho	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*
IPS	0.70	0.08	0.68	0.10	0.17	0.67	0.16	0.68
GC	0.76	<0.05	0.54	0.22	0.35	0.35	0.27	0.48
SDMT, T-score	0.76	<0.05	0.14	0.76	0.41	0.27	0.48	0.19
Stroop-W, T-score	0.20	0.67	0.61	0.15	-0.30	0.43	-0.50	0.18
EF	0.13	0.79	-0.54	0.22	0.72	<0.05	0.47	0.20
Stroop-I, T-score	-0.12	0.80	-0.67	0.10	0.76	<0.05	0.26	0.50
PASAT 3", T-score	0.18	0.70	-0.14	0.76	0.23	0.55	0.14	0.73

Note. PRO_{EF}=patient-reported executive function, PRO_{GC}=patient-reported general cognitive symptoms, EF=executive function composite, GC=general cognitive composite, IPS=information processing speed composite, Stroop-I=Stroop Color Word Test Color Word interference score, PASAT 3"=Paced Auditory Serial Addition Test (3-second version), SDMT=Symbol Digit Modalities Test, Stroop-W=Stroop Colour Word Test Word Reading Trial score, *p*=two-tailed *p*-value, *rho*=zero-order Spearman's correlation coefficient, N=sample size Note. PRO_{EF} and PRO_{GC} were analyzed as T-scores, whereas EF, GC, and IPS composites are calculated from cognitive test T-scores.

Table 2.6 Correlations Between Retinal Biomarkers, Cognitive PROs, and Insight

Retinal Biomarker (μm)	PRO_{EF}		PRO_{GC}		I_{EF}		I_{GC}	
	rho	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*
pRNFL (N_{MS}=6)	0.46	0.36	-0.12	0.83	-0.52	0.29	0.12	0.83
pRNFL (N_C=7)	-0.07	0.88	0.20	0.67	0.50	0.25	0.25	0.59
GCIPL (N_{MS}=6)	0.64	0.17	0.60	0.21	-0.71	0.11	-0.60	0.21
GCIPL (N_C=8)	0.12	0.78	0.21	0.63	0.26	0.53	0.02	0.96

Note. pRNFL=peripapillary retinal nerve fiber layer, GCIPL=ganglion cell and inner plexiform layer, PRO_{EF}=patient-reported executive function, PRO_{GC}=patient-reported general cognitive symptoms, I_{GC}=general cognitive insight, I_{EF}=executive function insight, *rho*=spearman's correlation coefficient, *p*=two-tailed *p*-value, N=sample size of controls or participants with MS as denoted with a C or an MS subscript.

Note. PRO_{EF} and PRO_{GC} were analyzed as T-scores.

Note. I_{EF} and I_{GC} reflect discrepancies between cognitive PRO and cognitive composite T-scores (additional details in Table 1).

Supplementary Table 2.1 OCT Quality Assessment

	pRNFL	GCIPL
Scans Included	60/169	23/29
Scans Excluded	109/169	6/29
Participants Excluded	2	2
	Number of Scans Excluded due to each OSCAR-IB criterion. Scans may be excluded for multiple reasons.	
Obvious	19	0
Insufficient Signal Strength	3	1
Ring not Centered	49	0
Algorithm Failure	0*	0*
Non-MS Retinal Pathology	18	4
Insufficient Illumination	10	2
Measurement Beam not Centrally Placed	28	0
	Details on how "Obvious" and "Non-MS-Retinal Pathology" Criteria were met	
Obvious	- 6 Scans were excluded because pRNFL thickness measurement was absent. - 13 Scans were excluded due to central artefacts (shadows cast onto the retina, likely caused by e.g., prominent floaters, eyelashes/eyelids, breakages in tear film)	- 0 Cases

	pRNFL	GCIPL
Non-MS Pathology	- 1 Participant had both eyes excluded from analyses for having SR SLE and SR glaucoma in addition to evident optic disc cupping. - 1 Participant had an eye excluded for having a retinal naevus. - 1 Participant had an eye excluded for having SR a history of a retinal detachment and vitrectomy. - 1 Participant had an eye excluded for having SR a previous retinal tear and related surgery. This participant had visible evidence of a previous retinal trauma in the affected eye (epiretinal membrane).	
	Details on eyes excluded due to previous ON	
Total Number of Participants Included After Excluding Eyes due to ON	13	14
Number of Eyes Excluded due to Previous Unilateral SR ON	1	
Number of Eyes Excluded due to a Suspected Previous Unilateral ON (Inter-Retinal Asymmetry)	2[1]	

	pRNFL	GCIPL
Number of Participants Excluded due to Previous Bilateral SR ON	1[2]	

Note. MS=participant with MS, ON=optic neuritis, SLE=systemic lupus erythematosus, SR= self-reported, pRNFL=peripapillary retinal nerve fibre layer, GCIPL=ganglion cell and inner plexiform layer, OCT=optical coherence tomography

*Note that scans were not excluded due to faulty segmentation. These scans were manually adjusted.

(1) Note that two participants had a suspected previous ON and of these two, one had also SR previous unilateral ON.

(2) Note that 1 participant was also excluded due to having previous SR bilateral ON, SR glaucoma (with optic disc cupping evident in scan), and SR SLE.

Supplementary Table 2.2 Conversion Table Used for Education in Generating Stroop T-scores

Ordinal Level of Education	**Continuous Level of Education**
Partial secondary/ high school or less	10.0 years
Secondary school/ high school diploma or equivalent	12.0 years
College or other non-university diploma or equivalent	13.0 years
University bachelor's degree or equivalent	16.0 years
University master's degree or equivalent	18.0 years
University PhD or equivalent	22.0 years

Chapter 3: Study 2

Cardiorespiratory Fitness is Related to Patient-Reported Cognition in People with Multiple Sclerosis: Might Fitness Promote Self-Awareness of Cognitive Function?

Abstract

Background: Cognitive impairment commonly affects persons with multiple sclerosis (MS). Cardiorespiratory fitness (CRF), as a marker of physical activity and exercise, has been associated with preserved cognitive performance in MS. It is unclear if these CRF-associated effects apply to patient-reported outcomes (PROs) – patient-centered, ecological indicators of function. This study examined the relationship between cognitive PROs and CRF in MS.

Methods: CRF was assessed as the peak volume of oxygen uptake during incremental cardiopulmonary exercise testing. Patient-reported general cognition (PRO_{GC}) and executive function (PRO_{EF}) were evaluated via Quality of Life in Neurological Disorders questionnaires. Cognitive performance was measured using the Symbol Digit Modalities Test (SDMT), Paced Auditory Serial Addition Test (PASAT), and the Stroop Colour and Word Test. Discrepancy scores between cognitive performance and PRO T-scores provided indices of insight (i.e., self-awareness of deficit). Relationships between CRF, cognitive PROs, insight, and cognitive performance were quantified via Spearman's correlation coefficients.

Results: Analyses of MS (n=7) and control samples (n=9) revealed that CRF was correlated with cognitive PROs and insight only in the MS group. Namely, higher CRF corresponded with overestimations of cognitive impairment in the MS sample with collectively unimpaired cognition. Overestimators of impairment that had MS exhibited unimpaired Stroop T-scores and some of the lowest SDMT T-scores.

Conclusion: Preliminary results indicate that higher CRF in MS is associated with elevations in patient-reported cognitive dysfunction. Findings may be due to CRF preserving EF and overestimators with MS demonstrating potentially heightened insight. Replication of findings in larger, diverse samples is needed.

Introduction

Approximately 40-70% of people with multiple sclerosis (MS) experience cognitive impairment (CI; 1), commonly reflected as impaired information processing speed (IPS), executive function (EF), and memory acquisition/encoding (2). The artificial clinical contexts in which cognitive tests are administered may limit their capacity to detect the real-world dysfunction that can be experienced in complex, everyday environments (3). Patient-reported outcomes (PROs) of cognitive functioning may complement neuropsychological testing to provide a more comprehensive picture of cognitive functioning in people with MS. Indeed, patient-reported general cognition (PRO_{GC}) has been observed to relate to thalamic and cortical atrophy in people with MS (4). Importantly, PRO_{GC} and PROs of memory (PRO_{memory}) have been reported to predict employment status and reduction in work hours (i.e., ecological indicators of functioning) above the effects of cognitive test performance in people with MS (5).

PRO_{GC} in people with MS has been documented to predict IPS and memory test performance independently of mood, disability, fatigue, and age (6). That being said, relationships between subjective and objective cognition seem to be somewhat domain-specific. PRO_{GC} (7,8), PRO_{memory} (9,10), and PROs of IPS (11), for example, often exhibit negligible-small relationships to cognitive performance in MS. Comparatively, PROs of EF (PRO_{EF}) are typically reported to have moderate-large relationships with cognitive performance in people with MS (7,12–14). Apparent domain-specific associations between objective and subjective cognition highlight plausibly meaningful distinctions between domains of subjective cognition. The possibility of different domains of subjective cognition gauging different components of real-world functioning underscores the value of studying domain-specific associations between patient-reported cognition and interventions/intervention targets for MS-related CI.

There is lacking reproducible and compelling evidence for the efficacy of pharmacological treatment options for MS-related CI (15). As such, interest has mounted in behavioral approaches for the management/treatment of CI in people with MS (16). Given the cognitive benefits of exercise in the general population (17), efforts have been made to understand the cognitive effects associated with exercise and physical activity in MS (16,18). One systematic review suggests the reported effects of physical activity and the maintenance of fitness on cognition are mixed but generally positive (18).

Cardiorespiratory fitness (CRF) reflects the capacity to deliver, extract, and use oxygen for physical activity mediated by aerobic metabolism (19), and can be used as an indicator of exercise status. A previous review reported positive associations between CRF and cognitive performance in people with MS (18). In particular, Sandroff et al., (2016; 18) reported that 6/6 of the reviewed publications that examined the association between CRF and cognition reported that higher CRF coincided with faster IPS in people with MS.

Given that IPS CI is the most prevalent manifestation of CI in people with MS (2), literature addressing the potential of exercise in managing other cognitive functions in MS is less extensive. One study in MS reported that CRF was related to IPS but not to composite measures of general cognitive function, verbal fluency, or memory (20). However, previous research on the association between CRF and EF in people with MS reported that CRF was related to interference control and cognitive flexibility, such that, individuals with greater CRF had faster responses to test stimuli (21,22). Other evidence indicates that the relationship between CRF and EF in MS is pronounced in people with impaired IPS and nullified in people with preserved IPS (23).

There exists literature indicating that exercise and CRF offer potential avenues and targets, respectively, for managing and rehabilitating MS-related CI (16,18). However, there is a dearth of research on the protective effects of CRF for ecological indicators of cognitive functioning, such as cognitive PROs. Therefore, the present research aimed to address the degree to which cognitive PROs are associated with CRF in people with MS. It was hypothesized that cognitive PROs would positively correlate with CRF in people with MS.

Methods

Participants and Recruitment

The current analysis involves baseline data from an ongoing study on the acute neuroplastic effects of exercise and non-invasive brain stimulation. The primary study entails a baseline visit and three follow-up visits interspaced by approximately one week. The ongoing study obtained approval by the University of Ottawa (H-11-21-7484) and Université du Québec en Outaouais research ethics boards.

Recruitment involved social media and flyer distribution via local MS and community-based outlets. Participants were required to be: 18-75 years old; able to communicate in English; willing to complete sessions at the Universities of Ottawa and Québec; asymptomatic according to the Get Active Questionnaire (24); and able to perform recumbent leg cycling. Participants with MS were also required to have a(n) Expanded Disability Status Scale (EDSS) score (25) between 3.0-7.0 (i.e., moderate-severe disability), self-reported diagnosis of MS, no relapses within the last 30 days, and stable disease modifying therapy treatment for the past six months. Individuals were excluded if they reported contraindications to receive non-invasive brain stimulation (26,27), had moderate-severe CI (2 or 3 on self-reported EDSS cognitive score; 28), or were pregnant.

Procedure

Participants were asked to refrain from caffeine, alcohol, tobacco, and exercise for 12 hours prior to their baseline assessments. Participants underwent cognitive testing, then a Neurostatus examination for generating an EDSS score (25), followed by incremental cardiopulmonary exercise testing to determine CRF. Participants received take-home, printed, English versions of self-reported outcomes and returned their completed questionnaires at a later visit.

Outcome Measures

Cognitive Performance

Cognitive tests were administered manually in a quiet room. Descriptions of cognitive tests are presented in Table 3.1. In order of administration, tests included the oral Symbol Digit Modalities Test (SDMT; 29), Stroop Colour and Word Test (30), and 3-second Paced Auditory Serial Addition Test (PASAT 3"; 31). Using T-scores from cognitive tests, IPS, EF, and general cognitive (GC) composites were calculated per Table 3.2. The SDMT was used as the primary measure of IPS. The Stroop interference score (Stroop-I) was used to measure interference control, a component of EF (32). The PASAT 3" was used to measure working memory, a facet of EF (32).

T-scores from cognitive tests were derived from normative data (30,33). Because the discrete norms for the PASAT 3" and the SDMT were created with adults, ages 18-65 years old, 51-65 age group norms were applied to participants 51-75 years old. Stroop normative data (30) quantified education on a ratio scale whereas the present study measured education ordinally. Participants' reported education levels were converted as follows in calculating Stroop T-scores: Partial secondary/ high school or less (10 years); Secondary school/ high school diploma or

equivalent (12 years); College or other non-university diploma or equivalent (13 years); University bachelor's degree or equivalent (16 years); University master's degree or equivalent (18 years); University PhD or equivalent (22 years). Impairment was considered performance -1.5 SD (≤35T) below one's demographic mean, a commonly applied threshold (3).

Patient-Reported Cognition

The Quality of Life in Neurological Disorders (Neuro-QOL) V 1.0-applied cognition-general concerns (GC) and V 1.0-applied cognition-executive function (EF) short forms (34,35) measured PRO_{GC} and PRO_{EF}, respectively. The 8-item NeuroQOL GC assesses difficulties with memory, attention, and decision-making, whereas the 8-item NeuroQOL EF measures complaints regarding one's application of executive abilities. Items on the NeuroQOL GC are answered on a 5-point scale ranging from 1 *(Very often / several times a day)* to 5 (*Never*). Items on the NeuroQOL EF are answered on a 5-point scale ranging from 1 (*Cannot do)* to 5 (*None*). Lower scores on these measures reflect greater perceived difficulty with cognitive functioning in daily life. Raw scores were summed and converted into T-scores using tables 4 and 5 from the Neuro-QOL V 5.0 scoring manual (36).

Insight

To gauge whether participant cognitive PROs indicated greater/equivalent/less CI in daily life than was detected using cognitive performance testing, discrepancy scores were calculated between objective cognitive composite scores and cognitive PRO T-scores (Table 3.2; similarly to 5,14). Resultant discrepancy scores were referred to as 'insight' of general cognition (I_{GC}) and EF (I_{EF}). Using thresholds from Smith & Arnett (2010; 14), participants with discrepancy scores $\leq 25^{th}$ and $\geq 75^{th}$ percentile of the control group's discrepancy scores were categorized as "under-estimators" and "over-estimators" of CI, respectively. The remaining participants were

considered accurate estimators of CI. Assuming each PRO and its corresponding composite reflect the same underlying construct (e.g., PRO_{GC} and GC reflect global cognitive function), greater positive discrepancy scores reflect a participant reporting more CI than would be anticipated from cognitive testing (Table 3.2). Conversely, lower negative scores reflect less reported CI than would be anticipated from cognitive testing.

Fatigue and Depression

The 9-item Fatigue Severity Scale (FSS; 37) measured symptoms of fatigue in the past week. The FSS contains items rated from 1 (*strongly disagree*) to 7 (*strongly agree*). Total scores on the FSS range from 1-7, calculated as the mean response across items. Greater scores reflect more fatigue. The depression subscale from the Hospital Anxiety and Depression Scale (HADS; 38) measured depressive symptoms in the past two weeks using seven 4-point items ranging between 0 *(Not at all)* and 3 (*Most of the time*). Scores on the depression subscale range from 0-21with greater scores representing more symptoms.

MS Disability

Disability was assessed via EDSS score (25) determined from a clinical examination performed by a Neurostatus-certified assessor. Scores on the EDSS range between 0 (*no neurological disability*) and 10 (*death due to MS*).

Fitness

Cardiorespiratory fitness (CRF) was measured via indirect calorimetry as the peak volume of oxygen uptake (VO_{2peak}) averaged across 20-second intervals (mlO_2/kg/minute) during incremental cardiopulmonary exercise testing on a recumbent stepper (SCIFIT Systems Inc). Silicon masks were fitted to participants to collect respired gases which were analyzed using a TrueOne 2400, ParvoMedics metabolic measurement system (Sandy, UT). The volume

of oxygen uptake (VO_2), carbon dioxide production (CO_2), and respiratory exchange ratio (RER) were measured continuously throughout the exercise test. Heart rate (HR, beats/minute) was measured continuously with a Polar (Polar Electro, Kempele, Finland) heart rate monitor. Participants subjectively appraised their exercise intensity each minute using the Borg Rating of Perceived Exertion (RPE; 39) scale. The initial work rate (WR) ranged from 0-20 Watts. WR increased by 5-20 Watt increments each minute until volitional fatigue (i.e., the participant indicated they were unable to continue exercising). This was followed by a 5-minute cool-down.

Clinical Characteristics and Demographics

Demographics and clinical characteristics were recorded using intake questionnaires.

Data Analysis

Analyses were conducted using IBM SPSS Statistics Version 29 (Armonk, NY). Between-group differences in sample characteristics and primary outcomes were analyzed via Cohen's *d* effect sizes and independent samples *t*-tests. Preliminary Spearman's correlations tested covariates (i.e., demographics, clinical characteristics, fatigue, and depression) of cognitive PROs and CRF. Potential covariates tested did not correlate with primary outcomes at the level of statistical significance ($p<0.05$) and hence were not controlled for in the following analyses. Hypothesized correlations between CRF and cognitive PROs were examined using Spearman's correlation coefficients (*rho*). To ground the interpretation of the relationship between CRF and cognitive PROs, exploratory correlations were conducted between CRF/cognitive PROs and cognitive performance and insight. Statistical significance was determined at the $p<0.05$ level (two-tailed).

Results

Sample Characteristics

Descriptive statistics for clinical, symptomatic, and demographic variables are reported in Table 3.3. The MS group had a mild-moderate level of EDSS disability (MDN=3.50, IQR=1.00) and most participants reported a progressive disease course (71%). The MS sample endorsed more depressive symptoms than controls by a small, not statistically significant degree (d=0.32, p=0.54). People with MS reported more fatigue than controls (d=1.65, p=0.01). The MS group (M=53.75, SD=13.24) was 13 years older than the control group (M=40.75, SD=17.70; d=0.81, p=0.09). Most participants with MS reported being female (71%) and 100% reported being Caucasian with a bachelor's degree or higher. Comparatively, 33% of controls were female, 22% reported being Caucasian, and 78% reported having a bachelor's degree or higher.

Descriptive statistics for cognition and fitness are reported in Table 3.4. There were no statistically significant differences between participants with MS and controls in terms of cognitive PRO or cognitive performance T-scores. However, the MS group had significantly lower CRF than controls (d=1.38, p=0.02).

Cardiorespiratory Fitness in Relation to Cognitive Performance and Cognitive PROs

CRF was not significantly correlated with any cognitive performance metric in either group (Table 3.5). The magnitudes of these associations were negligible-small for the SDMT and the PASAT 3” in both groups (rho<|0.30|) whereas coefficients were moderate-large between CRF and Stroop-I in the control (rho=0.46) and MS (rho=0.51) groups.

Correlations between CRF and cognitive PROs are shown in Table 3.5. In participants with MS, relationships between CRF and PRO_{EF} (rho=-0.83, p=0.02) and PRO_{GC} (rho=-0.93, p<0.01) occurred in the opposite direction than was hypothesized. In both cases, higher fitness

was associated with worse patient-reported cognition in participants with MS. In contrast, there were negligible-moderate, but not statistically significant correlations between CRF and PRO_{EF} (*rho*=0.02) and PRO_{GC} (*rho*=-0.42) in controls.

Correlations Between Cardiorespiratory Fitness and Insight

CRF was correlated with I_{EF} (*rho*=0.82, *p*=0.02) and I_{GC} (*rho*=0.93, *p*<0.01) in participants with MS (Table 3.5), suggesting that higher CRF was associated with elevated patient-reported CI relative to one's cognitive test performance. In comparison, correlations between CRF and I_{EF} (*rho*=0.12) and I_{GC} (*rho*=0.25) were small and non-significant in controls. Participants with MS were rank-ordered *post hoc* according to their CRF (Table 3.6) to examine CRF with respect to cognitive performance and insight and to better interpret this finding. This process revealed that participants with MS of the highest CRF overestimated EF and GC CI, had intact Stroop-I T-scores, and had some of the lowest SDMT T-scores among the MS group.

Discussion

CRF is associated with maintained brain structure (40,41) and cognition in people with MS (18). Despite this, and contrary to what was hypothesized, negative correlations were observed between CRF and cognitive PROs in the MS group, such that higher CRF corresponded with elevated reports of dysfunction in daily life. In the MS sample, positive correlations were observed between CRF and insight – indicating that higher CRF was associated with overestimations of CI relative to one's cognitive performance. These findings were specific to the MS group as CRF was not correlated with cognitive PROs or insight in controls. Because overestimators of CI with MS demonstrated intact Stroop-I performances and some of the lowest SDMT performances, findings might be explainable by higher CRF coinciding with intact executive precursors to insight. To our knowledge, this is the first

documented evidence that fitness is related to cognitive PROs and insight in a neuropsychological population, however, these initial findings need to be replicated and expanded. Research demonstrating that exercise training/ physical activity can promote insight could have implications for exercise prescription intended to prevent loss of insight and maintain functional independence or to complement cognitive rehabilitation.

In the current study, CRF did not display statistically significant relationships with cognitive performance in participants with MS who, as a group, did not exhibit CI. This result aligns with research indicating that the relationship between CRF and cognition loses statistical significance in MS samples that have unimpaired cognition at the group-level (23).

Research has reported better PRO_{memory} to be associated with more frequent/strenuous physical activity in people with MS (42). However, physical activity has been observed to be unrelated or weakly related to better PRO_{GC} (42,43), except in people with MS who engage in moderate-high levels of physical activity (44). Findings herein concerning the MS sample depart from these previous studies as higher CRF was related to worse PRO_{EF} and PRO_{GC}. Likewise, in the MS group alone, CRF correlated with insight, such that, those with greater CRF tended to 'overestimate' CI. However, 'overestimation' in this context should be interpreted carefully as overestimators with MS demonstrated intact Stroop-I T-scores and some of the lowest SDMT T-scores among the MS group. Hence, these participants' reports may reflect indications of cognitive dysfunction in daily life arising from subtle IPS decrements. Together, this pattern of observations may suggest that higher CRF is potentially associated with hypernosognosia in people with MS. Hypernosognosia describes increased self-awareness of cognitive decline and has been documented in the preclinical (i.e., subjective cognitive decline) and prodromal (mild cognitive impairment) stages of Alzheimer's disease (45,46).

Unawareness of neuropsychiatric/neurologic deficits (i.e., anosognosia) in various conditions typically occurs concurrently with pathologies of the prefrontal, medial temporal, and parietal cortices (45,47,48) and executive dysfunction (47,49–51). Although the substrate(s) of insight deficits have yet to be studied in people with MS, the degree of CI insight coincides with the integrity of EF in people with MS (52,53). Considering that overestimators with MS had some of the highest Stroop-I performances, the correlation between CRF and insight in the MS group lends itself to the following explanation. Perhaps higher CRF is associated with preserved insight in MS as a byproduct of the maintenance of CRF preserving EF or components of EF. Indeed, there is observational evidence supporting the protective effects of CRF for EF in people with MS (21,22). Although the correlation between CRF and Stroop-I was not statistically significant herein, the effect size of this relationship was much larger than those between CRF and the SDMT or the PASAT 3". In any case, a firm mechanistic account of why a relationship between CRF and insight may exist in people with MS is beyond the scope of what may be induced from this study.

The clinical relevance of the finding that CRF is related to insight is underscored by the assumption that one's ability to monitor their health is a prerequisite to seeking care for a given problem. Insight of cognitive symptoms may be paramount to an individual with MS seeking neuropsychological assessment and cognitive rehabilitation. Furthermore, insight is thought to maintain a role in the compensation of cognitive decline, for example, by allowing one to implement adaptive strategies (50). Indeed, this sentiment is empirically supported insofar as older adults implement cognitive strategies vis-à-vis their awareness of their cognitive decline (54). In people with CI due to Alzheimer's disease, anosognosia is related to adverse outcomes such as reduced medication adherence, heightened risk of vehicular accidents, and increased

caregiver burden (50). In people with MS, insight deficits have been associated with reduced quality of life and ability to perform instrumental activities of daily living (55). That being said, future research should longitudinally/experimentally elaborate on the current findings by investigating the potential of fitness/exercise to maintain/rehabilitate insight. Identifying exercise targets to preserve/improve insight may be pivotal to incorporating exercise recommendations into patient care – specifically, in relation to cognitive rehabilitation, and broadly, in relation to the maintenance/recovery of functional independence in people with MS.

Strengths and Limitations

A strength of this study is that findings were contextualized with respect to the sample's cognitive performance. Previous MS literature on physical activity and cognitive PROs (42–44) failed to consider how cognitive status may alter insight (47,49–53,56) and the cognition-fitness relationship (23).

This research was limited in multiple regards. First, the sample was small, and results should thus be taken as preliminary. Second, considering that 100% of participants with MS were Caucasian and had at least a bachelor's degree, the generalizability of the current findings is limited by ethnic, socioeconomic, and cultural sample homogeneity. Third, this research is limited for not having a more robust battery to measure GC, EF, and other cognitive functions.

In addition to being limited by study-specific features, the present study was limited methodologically based on its operationalization of underestimation/overestimation. The classification of participants as overestimators and underestimators was guided by methods of studying insight in people with MS (5,14). This approach of creating discrepancy score cut-offs was especially limited in the current analysis considering the size of the control group. Broadly speaking, however, this approach of obtaining cut-offs from a given study's sample distribution

of discrepancy scores is further limited insofar as it prevents a common criterion of overestimation/underestimation being used across studies. A common criterion of overestimation/underestimation could facilitate the interpretability of and comparability across research on insight in people with MS and other conditions. Research on insight could hence be strengthened if there existed normative data on cognitive discrepancy scores and population-based cut-offs for determining overestimation/underestimation.

Conclusion

Given that previous literature indicates that the maintenance of CRF may contribute to the preservation of objectively measured cognition in people with MS (18,21–23), the present study examined whether such effects were evident in cognitive PROs. This study found evidence that higher CRF in people with MS is associated with elevated patient-reported EF and GC dysfunction. Additionally, the presented preliminary results indicate that higher CRF in MS is correlated with overestimations of EF and GC dysfunction relative to one's tested cognitive performance. Notably, overestimators of CI with MS exhibited some of the highest Stroop-I performances and lowest SDMT performances among the MS group. The correlation between higher CRF and patient-reported cognitive dysfunction in people with MS might be explained by higher CRF being associated with hypernosognosia – heightened insight of pathological cognitive decline. Replication of these findings in larger, diverse MS samples and people with other conditions is needed. Evidence that exercise targets could maintain insight or facilitate its recovery could have important implications for promoting functional independence and facilitating cognitive rehabilitation.

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Table 3.1 Summary of Cognitive Outcomes

Outcome Name	Outcome Description
SDMT	Raw scores reflect the number of appropriate matches made between geometric symbols with digits (1-9) within 90 seconds using a key.
Stroop	Raw scores reflect the amount of stimuli appropriately processed (given task demands) in a 45-second-long trial.
Stroop-W	Word score: number of words read aloud “red”, “green”, “blue”, (Stroop trial 1).
Stroop-C	Colour score: number of stimuli colours named aloud (Stroop trial 2). Stimuli were coloured red, green, or blue.
Stroop-CW	Colour-word score: number of the incongruent ink colours named aloud for the words “red”, “green”, “blue” (Stroop trial 3).
Stroop-I	Scores were calculated using all trial scores per Golden & Freshwater (2002) (145).
PASAT 3”	Raw scores reflect the total number of correct responses made aloud. The PASAT 3” requires participants to summate single digits presented every three seconds for 60 summations.
Neuro-QOL GC	Questionnaire of patient-reported general cognitive ability.
Neuro-QOL EF	Questionnaire of patient-reported executive function.

Note. SDMT=Symbol Digit Modalities Test, Stroop=Stroop Colour Word Test, PASAT 3”= Paced Auditory Serial Addition Test, Neuro-QOL EF=Neuro-QOL item bank V 1.0-applied cognition-executive function, Neuro-QOL GC=Neuro-QOL item bank V 1.0-applied cognition-general concerns.

Table 3.2 Operationalization of Insight

Cognitive Domain	Cognitive Performance	Patient-Reported Cognition	Insight
Executive Functions	EF=[(Stroop-I) + (PASAT 3")]/2	PRO_{EF}=Neuro-QOL EF	I_{EF}=[(EF) – (PRO_{EF})]
Processing Speed	IPS=[(SDMT) + (Stroop-W)]/2		
General	GC=[(IPS)+(EF)]/2	PRO_{GC}=Neuro-QOL GC	I_{GC}=[(GC) – (PRO_{GC})]
		Insight Groups	
		UE-CI=I ≤ 25th%ile OE-CI=I ≥ 75th%ile	

Note. EF=Executive Composite, GC=General Cognitive Composite, IPS=Information Processing Speed Composite, SDMT=Symbol Digit Modalities Test, Stroop-W=Stroop Color Word Test Word Reading score, Stroop-I=Stroop Color Word Test Color Word Interference Control score, PASAT 3"=Paced Auditory Serial Addition Test, PRO_{EF}=patient-reported executive function, Neuro-QOL EF=Neuro-QOL item bank V 1.0-applied cognition-executive function. PRO_{GC}=patient-reported general cognitive symptoms Neuro-QOL GC=Neuro-QOL item bank V 1.0-applied cognition-general concerns, I=Insight, UE-CI=Underestimation of cognitive impairment, OE-CI=Overestimation cognitive impairment.

Note. Stroop, PASAT 3", SDMT and cognitive PRO metrics used in the above composite score calculations reflect T-scores.

Table 3.3 Sample Descriptive Statistics: Demographics, Clinical Characteristics, Fatigue, and Depressive Symptoms

Characteristic	MS (N=7)		Control (N=9)			
	Mean	SD	Mean	SD	*p*	*d*
Age	53.75	13.24	40.75	17.70	0.09	0.81
	N	%	N	%		
Sex (% Female)	5	71	3	33		
Race						
Asian	0	0	1	11		
African	0	0	2	22		
Caucasian	7	100	2	22		
Indigenous	0	0	1	11		
Latino	0	0	1	11		
Other	0	0	1	11		
Unknown	0	0	1	11		
Education						
High School Diploma/Equivalent	0	0	1	11		
College Diploma/ Equivalent	0	0	1	11		
University Bachelor/Equivalent	4	57	0	0		
University Masters Degree/Equivalent	2	29	5	56		
University PhD/Equivalent	1	14	2	22		
	MDN	IQR	MDN	IQR		
EDSS	3.50	3.00-4.00	--	--		
	Mean	SD	Mean	SD		
Disease Duration (yrs)	9.33	9.20	--	--		
Clinical course	N	%	N	%		
RRMS	2	29	--	--		
SPMS	1	14	--	--		
PPMS	4	57	--	--		
Symptoms	Mean	SD	Mean	SD	*p*	*d*
HADS (Depression)	7.29	5.22	5.67	5.08	0.54	0.32
FSS	5.27	1.80	2.63	1.43	0.01	1.65

Note. EDSS=Expanded Disability Status Scale, RRMS=relapsing remitting multiple sclerosis subtype, SPMS=secondary progressive multiple sclerosis subtype, PPMS=primary progressive multiple sclerosis subtype, HADS=depression subscale of the Hospital Anxiety and Depression Scale, FSS=Fatigue Severity Scale, MDN=median, SD=standard deviation, IQR=interquartile range, N=sample size, %=percentage of participants.

Table 3.4 Sample Descriptive Statistics: Cognitive Outcomes and Fitness

Cognitive Outcome	MS (N=7)		Controls (N=9)			
	Mean	SD	Mean	SD	*p*	*d*
Raw SDMT	53.16	7.57	63.83	13.65		
SDMT, T-score	44.70	8.09	51.30	12.53	0.21	-0.60
Raw PASAT 3”	50.75	5.97	52.08	5.85		
PASAT 3”, T-score	53.24	5.47	54.98	6.78	0.55	-0.28
Stroop-I, T-score	56.75	7.38	59.17	5.98	0.43	-0.37
PRO_{EF}	44.31	10.31	43.09	9.66	0.81	0.12
PRO_{GC}	40.53	11.19	44.44	9.72	0.47	-0.38
$VO_{2\ peak}$	25.74	4.20	39.05	12.19	0.02	-1.38

Note. SDMT=Symbol Digit Modalities Test, PASAT 3”=Paced Auditory Serial Addition Test (3-second version), Stroop-I=Stroop Color Word Test Color Word Interference Score, PRO_{EF}=patient-reported executive function, PRO_{GC}=patient-reported general cognitive symptoms, VO_{2peak}=peak volume of oxygen uptake in mlO_2/kg/minute, MS=participants with multiple sclerosis, SD=standard deviation, N=sample size, *p*=two-tailed significance of independent sample *t*-test, *d*=Cohen’s *d* effect size.

Note. Cognitive PROs are reported in T-scores.

Table 3.5 Correlations between Cardiorespiratory Fitness and Cognitive Outcomes

Cognitive Outcome	VO_{2peak} (N_{MS}=7)		$VO_{2\ peak}$ (N_C=9)	
	rho	*p*	*rho*	*p*
Cognitive Performance				
SDMT, T-score	-0.29	0.54	-0.12	0.77
PASAT 3", T-score	0.00	0.99	-0.06	0.88
Stroop-I, T-score	0.51	0.25	0.46	0.21
Patient-Reported Cognition				
PRO_{EF}	-0.83	0.02	0.02	0.97
PRO_{GC}	-0.93	<0.01	-0.42	0.27
Insight				
I_{EF}	0.82	0.02	0.12	0.77
I_{GC}	0.93	<0.01	0.25	0.52

Note. $VO_{2\ peak}$=peak oxygen volume uptake in mlO_2/kg/minute, SDMT=Symbol Digit Modalities Test, PASAT 3"=Paced Auditory Serial Addition Test 3-second version, Stroop-I=Stroop Colour Word Test Interference score, PRO_{EF}=patient-reported executive function, PRO_{GC}=patient-reported general cognitive symptoms, I_{EF}=insight of executive function, I_{GC}=insight of general cognitive function, *rho*=Spearman's correlation coefficient, *p*=two-tailed *p*-value, N=sample size of controls or participants with MS as denoted with a C or an MS subscript.

Note. PRO_{EF} and PRO_{GC} were analyzed as T-scores.

Table 3.6 Rank-Ordering Participants with MS High-Low [1-7] Cardiorespiratory Fitness and Displaying their Cognitive Performance and Insight

CRF Rank	$VO_{2\ peak}$	Stroop-I, T-score	SDMT, T-score	I_{EF}	I_{GC}
1	30.91	61.00	42.26	20.13 ^{OE}	16.63 ^{OE}
2	30.13	68.00	45.71	23.78 ^{OE}	17.97 ^{OE}
3	27.30	57.00	27.83*	24.20 ^{OE}	12.96 ^{acc}
4	25.09	53.00	51.53	9.52 ^{UE}	11.34 ^{acc}
5	24.49	45.00	40.25	3.98 ^{UE}	-12.70 ^{UE}
6	23.69	63.00	52.66	2.08 ^{UE}	9.15 ^{acc}
7	18.59	57.00	50.31	-2.92 ^{UE}	-0.68 ^{UE}

Note. CRF=cardiorespiratory fitness, VO_{2peak}=peak volume of oxygen uptake in mlO_2/kg/minute, Stroop-I=Stroop Test interference control, SDMT=Symbol Digit Modalities Test, I_{EF}=insight of executive function, I_{GC}=insight of general cognition, UE=underestimate impairment, OE=overestimate impairment, acc=accurately estimate impairment.

Note. *Indicates that an individual met commonly employed threshold of CI (-1.5 SD; ≤35 T).

Chapter 4: Results Pertaining to Thesis Hypotheses

The following section presents a summary of thesis results in relation to thesis hypotheses. This section exists because hypotheses 1-4 were removed from Study 1 given the small size of the sample and analytical approach applied.

4.1 Hypothesis 1: PRO_{EF} and PRO_{GC} will more Strongly Correlate with EF Performance (EF in General, Interference Control in Particular) than GC or IPS Performance in People with MS

As depicted in Table 4.1, the observed correlation coefficients between cognitive PROs and cognitive test performance failed to support hypothesis 1. The coefficients between PRO_{GC} and executive (EF and Stroop-I; *rho*=-0.54, -0.67) and nonexecutive (IPS and GC; *rho*=0.68, 0.54) outcomes were all large. In contrast, coefficients between PRO_{EF} and cognitive performance were small for executive outcomes but large for non-executive outcomes (*rho*=0.13, -0.12 and 0.70, 0.76).

4.2 Hypothesis 2: Cognitive Performance (EF in General, Interference Control in Particular, IPS, and GC) will more Strongly Correlate with PRO_{EF} than PRO_{GC} in People with MS

As depicted in Table 4.1, the correlation coefficients between cognitive PROs and cognitive performance in participants with MS provide equivocal support for hypothesis 2. Coefficients between PRO_{GC} and cognitive performance (EF, Stroop-I, IPS, GC, respectively) were larger but more directionally varied (*rho*=-0.54, -0.67, 0.68, 0.54) than those between PRO_{EF} and cognitive performance (*rho*=0.13, -0.12, 0.70, 0.76).

4.2.1 Examining Hypotheses 1 and 2 in Controls

Although there were no *a priori* hypotheses regarding people without MS, Spearman's correlations were used to examine the relationships pertaining to hypotheses 1 and 2 in controls. In controls, hypotheses 1 and 2 were generally supported (Table 4.2). Concerning hypothesis 1, IPS had small correlation coefficients with PRO_{EF} and PRO_{GC} (*rho*=0.17, 0.16). The correlation coefficients between GC performance and PRO_{EF} and PRO_{GC} were small-moderate in effect size (*rho*=0.35, 0.27). In comparison, the correlation coefficients were small-large between executive measures (EF and Stroop-I) and PRO_{EF} (*rho*=0.72 and 0.76) and PRO_{GC} (*rho*=0.47 and 0.26). Concerning hypothesis 2, correlation coefficients between cognitive performance (EF, Stroop-I, IPS, GC) and PRO_{EF} (*rho*=0.72, 0.76, 0.17, 0.35) were larger than those between cognitive performance and PRO_{GC} (*rho*=0.47, 0.26, 0.16, 0.27).

4.3 Hypothesis 3: PRO_{EF}, PRO_{GC}, and Respective Insight will Positively Correlate with pRNFL and GCIPL Thickness in People with MS

In participants with MS the pattern of non-statistically significant correlations between PRO_{EF} and pRNFL (*rho*=0.46) and GCIPL (*rho*=0.64) thickness supported hypothesis 3 whereas coefficients between PRO_{GC} and pRNFL (*rho*=-0.12) and GCIPL (*rho*=0.60) thickness were less consistent in direction – thereby providing some, albeit less support for the hypothesized associations. That said, this pattern of correlations generally was in support of H4, that *retinal thickness (pRNFL and GCIPL) will more strongly correlate with PRO_{EF} than PRO_{GC} in people with MS.*

In the MS sample the pattern of not statistically significant relationships between insight (I_{GC} and I_{EF}) and retinal biomarkers (pRNFL and GCIPL) were contrary to the hypothesized effects with coefficients generally being large and negative (e.g., *rho*=-0.52, -0.60, -0.71). At

face value, the large, non-significant inverse relationship reported herein would be interpreted as underestimation and overestimation of CI being associated with preserved and degenerated neuroaxonal tissue, respectively. Importantly, the current sample of participants with MS did not contain anyone who technically underestimated CI, in other words, met thresholds of CI (e.g., <35T; 41) but indicated they were cognitively intact. A more appropriate interpretation of individuals herein classified as underestimators of CI might be that they simply had high appraisals of their ability, potentially due to high self-esteem or something of this nature. Importantly, this interpretation is speculative as this research measured specific self-appraisals (i.e., cognitive PROs) but it did not examine self-esteem or global self-appraisal. Nevertheless, in the absence of participants with true underestimation of CI, it was likely the case that overestimators of CI in the MS sample were the main contributors of the negative relationship between insight and retinal biomarkers of neuroaxonal degeneration. Therefore, an appropriate interpretation of this finding is: relative to accurate estimators of CI and overestimators of cognitive ability (i.e., underestimators), overestimators of CI had more neuroaxonal degeneration.

This finding strengthens the notion that overestimation of CI in people with MS is analogous to subjective cognitive decline (SCD) in people with preclinical Alzheimer's disease as studies have found that these disproportionate reports of cognitive dysfunction coincide with neuroradiological markers of disease pathology (140,141).

4.4 Exploratory Analysis on the Relationship Between PRO_{EF}, PRO_{GC}, I_{EF}, I_{GC}, and Symptoms of Fatigue and Depression

Depressive symptoms were not correlated with either PRO_{EF} (*rho*=-0.02, *p*=0.97) or PRO_{GC} (*rho*=0.18, *p*=0.70) in the MS sample. Fatigue exhibited a large, non-statistically

significant correlation with PRO_{EF} (*rho*=-0.74, *p*=0.06) but not PRO_{GC} (*rho*=-0.36, *p*=0.43) in participants with MS. In controls, depressive symptoms did not correlate with PRO_{EF} (*rho*=-0.42, *p*=0.26) but demonstrated a large, non-statistically significant correlation with PRO_{GC} (*rho*=-0.65, *p*=0.06). That being said, fatigue was correlated with PRO_{EF} and PRO_{GC} in controls (*rho*=-0.75, -0.77; *p*=0.02, 0.02), suggesting that greater fatigue occurred in parallel with lower perceived cognitive function.

I_{EF} and I_{GC} were not correlated with fatigue (*rho*=0.46, 0.36; *p*=0.29, 0.43) or depressive symptoms (*rho*=-0.31, -0.18; *p*=0.50, 0.70) in the MS group. In controls, I_{EF} and I_{GC} displayed large, non-statistically significant correlations with fatigue (*rho*=0.63, 0.58; *p*=0.07, 0.10) and were correlated with depressive symptoms (*rho*=0.74, 0.87; *p*=0.02, 0.01), such that, as these symptoms increased, controls were more likely to overestimate CI. A potential reason for this finding could be as follows. In a population that is not experiencing pathological cognitive symptoms (e.g., controls), "mood-congruent bias" (142) or "cognitive impairment bias" (143) might disproportionately account for deviations in the reporting of cognitive ability and objectively measured cognitive performance. Conversely, in the MS sample that was likely experiencing pathological cognitive decline with minimal depression, reported cognitive symptoms might be more likely to reflect their genuine neurocognitive changes rather than overly negative self-appraisals.

4.5 Hypothesis 5: Cognitive PROs will Positively Correlate with CRF in People with MS

Findings did not support hypothesis 5 as higher CRF was associated with more patient-reported cognitive dysfunction (EF and GC; *rho*≤-0.83, *p*≤0.02) exclusively in participants with MS. Similarly, only in participants with MS was higher CRF associated with a tendency to overestimate CI. Since such overestimations coincided with high EF and slow IPS in the MS

sample, it was interpreted that higher CRF corresponded with potentially greater awareness of the initial stages of cognitive decline – hypernosognosia (140).

Table 4.1 Expected Versus Observed Correlations between Cognitive Metrics in the MS Sample (N=7)

	EF	Stroop-I	GC	IPS
	Hypothesized correlations			
PRO_{EF}				
PRO_{GC}				
	Observed correlations (*rho*)			
PRO_{EF}	+0.13	-0.12	+0.76*	+0.70
PRO_{GC}	-0.54	-0.67	+0.54	+0.68

Note. PRO_{EF}=patient-reported executive function, PRO_{GC}=patient-reported general cognition, EF=executive function, Stroop-I=Stroop test interference control score, GC=general cognitive function, IPS=information processing speed.

Note. Cells are saturated to help visualize the relative effect sizes of the anticipated and observed relationships.

Note. *Indicates result was statistically significant ($p<0.05$, two-tailed).

Note. Hypothesis 1: PRO_{EF} and PRO_{GC} will more strongly correlate with objective EF performance (EF in general and interference control in particular) than objective GC or IPS performance in people with MS.

Note. Hypothesis 2: Objective cognitive performance (EF in general, interference control in particular, IPS, and GC) will more strongly correlate with PRO_{EF} than PRO_{GC} in people with MS.

Table 4.2 Anticipated Versus Observed Associations between Cognitive Metrics in the Control Sample (N=9)

	EF	Stroop-I	GC	IPS
	hypothesized correlations			
PRO_{EF}				
PRO_{GC}				
	observed correlations			
PRO_{EF}	+0.72*	+0.76*	+0.35	+0.17
PRO_{GC}	+0.47	+0.26	+0.27	+0.16

Note. PRO_{EF}=patient-reported executive function, PRO_{GC}=patient-reported general cognition, EF=executive function, Stroop-I=Stroop test interference control score, GC=general cognitive function, IPS=information processing speed.

Note. Cells are saturated to help visualize the relative effect sizes of the anticipated and observed relationships.

Note. *Indicates result was statistically significant ($p<0.05$, two-tailed).

Note. Hypothesis 1: PRO_{EF} and PRO_{GC} will more strongly correlate with objective EF performance (EF in general and interference control in particular) than objective GC or IPS performance in people with MS.

Note. Hypothesis 2: Objective cognitive performance (EF in general, interference control in particular, IPS, and GC) will more strongly correlate with PRO_{EF} than PRO_{GC} in people with MS.

Chapter 5: Overarching Discussion

Cognitive PROs may provide insights into real-world cognitive function. Assessing patient experiences of neurological functioning can facilitate a better understanding of the cognitive effects of a disease or disease interventions (85). This thesis aimed to better understand: i) the neuropsychological utility and interpretation of cognitive PROs in MS; and ii) the potential protective effects on cognition associated with maintaining physiological fitness in MS. Study 1 examined correlations between features of patient-reported cognition and objective neuropsychological outcomes and putative confounds (i.e., depression and fatigue) in people with MS and controls. Study 2 examined associations between CRF and features of patient-reported cognition in people with MS and controls.

5.1 Summary and Discussion of Thesis Findings

Study 1 provided preliminary evidence that, in an early stage of MS-related cognitive decline, patient-reported cognition mirrors some of the objective neurocognitive changes that people with MS undergo. PRO_{EF} more strongly correlated with more affected cognitive (SDMT, GC, IPS) and radiological (GCIPL) outcomes relative to less affected cognitive (PASAT 3", Stroop-W, EF, Stroop-I) and radiological (pRNFL) outcomes in the MS sample. In the MS group, this pattern of coefficients persisted in the correlations between insight and radiological biomarkers; however, PRO_{GC} somewhat less consistently correlated with cognitive performance and radiological metrics per this less-more-affected pattern. These findings were unique to the MS group as cognitive PROs/insight did not correlate with cognitive performance and radiological biomarkers according to the gradient of less-more-affected MS outcomes.

Neither cognitive PRO correlated with depression and only PRO_{EF} was observed to have a large, non-statistically significant correlation with fatigue in the MS group. Insight metrics –

discrepancies between cognitive PROs and cognitive performance – were unrelated to depression and fatigue in the MS sample. Therefore, fatigue and depressive symptomatology were not supported to confound the accuracy of patient-reported cognition in this sample, which, at the group-level, minimally surpassed previously used thresholds to screen for depression (≥7; 144).

In contrast to what was anticipated, Study 2 found that CRF was inversely correlated with patient-reported cognition, such that higher CRF was associated with increased perceptions of everyday cognitive dysfunction in people with MS (but not in controls). Post-hoc examination revealed that higher CRF coincided with overestimation of CI. That being said, participants with MS who overestimated CI appeared to have intact EF in conjunction with more pronounced neurodegeneration and slowed IPS. Therefore, the relationship observed between CRF and overestimation of CI was interpreted as preliminary evidence that higher CRF may be associated with a state of heightened awareness of subtle cognitive changes, namely, the slowing of IPS.

Figures 5.1 and 5.2 are presented at the end of the current chapter to supplement concepts contained in the following discussion. In Particular, Figure 5.1 presents a model of patient-reported cognition as a function of one's level of cognitive ability in combination with their accrued cognitive decline/fatigability. Figure 5.2 adds to this model to illustrate how inter-individual differences in terms of premorbid function/cognitive reserve might influence one's likelihood of "overestimating", accurately estimating and underestimating CI in response to cognitive decline.

5.2 Between Being Cognitively Intact and Impaired – 'Preserved' Cognitive Function in the Face of Evident Neuropathology

Mean T-scores were unimpaired for all cognitive performance metrics in the MS group (i.e., T>35). That being said, the MS sample's cognitive performance was below the

demographic mean for tests of IPS (M T-SDMT=45; M T-Stroop-W=37) but not measures of EF, namely, working memory (M T-PASAT 3"=53) and interference control (M T-Stroop-I=57). Relative to controls, the MS group exhibited moderate-large but non-statistically significant reductions in axonal thickness (i.e., pRNFL, d=-0.81, p=0.08) and most cognitive performance metrics (i.e., Stroop-W, d=-0.57, p=0.25; SDMT, d=-0.60, p=0.21; GC, d=-0.86, p=-0.09; IPS, d=-0.93, p=0.07). The MS sample displayed significantly greater neurodegeneration (i.e., GCIPL, d=-1.63, p<0.05) relative to controls as measured on retinal OCT.

Neuroaxonal damage as measured using retinal OCT (i.e., GCIPL and pRNFL thickness) correlates with MRI measures of MS disease burden, such as lesion load, whole brain and regional atrophy of the thalamus, corpus callosum, insula, cerebral cortex, basal ganglia, caudate nucleus, and cingulate cortex (71,74,75,79,145–147). If OCT metrics offer valid markers of disease burden, the lower GCIPL and pRNFL (non-statistically significant) thicknesses observed in the MS sample compared to controls provide some evidence that disease processes may have degraded associated, cognitively relevant structures within this group. Indeed, relative to controls, the MS sample demonstrated slower IPS performance metrics (moderate-large effect sizes, non-statistically significant) – the earliest affected cognitive domain in MS (33,34). These slow performances, coupled with GCIPL and pRNFL thinning suggest this sample may be in an early stage of cognitive decline, where performance is generally unimpaired but has likely been reduced from a premorbid level of function.

5.2.1 Cognitive Reserve in Relation to Functional Compensation

In an effort to identify those on track to developing mild cognitive impairment (MCI) as a precursor to Alzheimer's disease (AD), the subjective cognitive decline (SCD) framework has characterized persons with self-perceived cognitive worsening but demographically normal

cognitive performance (90). In this paradigm, compensated cognition describes the semblance of intact cognition within the artificial constraints of cognitive testing despite neuropathology and theoretically reduced function that is not readily detectable via clinical assessment (90). Compensation (as described within the SCD framework) might be partially explained by mechanisms found within the theoretical model of cognitive reserve (discussed in *Section 1.2.3*).

Cognitive reserve describes inter-individual differences in the degree of resilience to neuropathology or aging in the form of maintained cognitive abilities (39,40). Arguably, individuals of high premorbid function and/or those who are especially capable of accommodating their cognitive decline (i.e., have high cognitive reserve) may be prone to endorsing SCD or 'overestimating' CI (Figure 5.2). That being said, the MS sample was of high formal education – a putative promoter of cognitive reserve (39,42) – thereby corroborating that the sample might have had an elevated reserve capacity for compensation and consequent risk of being classified as overestimators in the face of their decline.

Overestimation of MS-related CI might serve as a measure of the extent to which cognitive testing fails to grasp the effects of cognitive decline for which an individual is aware. This may be especially true in persons with little evidence of being influenced by putative confounds (e.g., depression). In the present MS sample, pRNFL thickness demonstrated a large, non-statistically significant correlation with insight of EF but not GC, whereas GCIPL thickness demonstrated large, non-statistically significant correlations with insight of EF and GC. These correlations were driven by participants "overestimating" CI having lower neuroaxonal thickness than participants accurately estimating or overestimating cognitive ability (i.e., classified as CI underestimators but not having CI). This finding is comparable to preclinical AD literature indicating that SCD preceding MCI is associated with elevated amyloid beta accumulation (140).

Conversely, underestimation of CI among people with aMCI has been observed to correspond with greater amyloid beta accumulation and risk for conversion to AD (140,148).

5.3 Patient-Reported Cognition in Relation to Depression and Fatigue

Fatigue and depression have been discussed as symptomatic variables that could limit the ability of people with MS to accurately respond to cognitive PROs (91–94). Indeed, patient-reported cognitive dysfunction has been observed to be more related to low self-esteem and elevated symptoms of depression and fatigue than to cognitive performance in people with MS (94–98). That being said, depression and fatigue have also been reported to maintain relationships with cognitive performance in people with MS (93,149,150). On the contrary, analyses herein found negligible-small, not statistically significant correlations between depressive symptoms and cognitive PROs/insight in the MS sample. Results may have deviated from previous literature (93–98,150) given that there was minimal influence of depression on the MS sample that only exhibited small, non-statistically significant elevations in depression. In comparison, analyses indicated moderate-large, but not statistically significant correlations between fatigue and cognitive PROs/insight in the MS sample with large, statistically significant elevations in fatigue.

Considering the following discussion, it stands to reason that symptoms of depression and fatigue share a complex relationship with patient-reported cognition and should not be viewed exclusively as confounds to the accuracy of cognitive PROs. Rather, depression and fatigue might be appropriately conceived of as covarying psychological responses to one's experience of CI, and/or occurring separately from MS-related CI but within a population where CI is common, and/or resulting directly from shared underlying MS neuropathology.

5.3.1 On the Relationship between Cognition and Depressive Symptomatology

The difficulty of making sense of the relationship between depressive symptoms and cognitive PROs in people with MS might first be addressed by considering the enigma of distinguishing symptoms of comorbid depression from those of MS (e.g., fatigue, disturbed sleep, self-reported cognitive symptoms; 149). Feinstein et al., (2014; 149) indicate that depression can be diagnosed in MS as: i) a psychological response to one's disease progression; ii) occurring independently from one's MS; or iii) a direct result of one's disease-related neuropathology. Notably, the neural correlates of depression in people with MS (ventricular, frontal and/or temporal lobe atrophy, parietal- and-fronto-cortical lesion load; 149), overlap with those of CI (discussed in *Section 1.3.1*). The coupling of depressive symptoms and cognitive deficits in people with MS along these three dimensions – namely, depression as a i) psychological reaction to disability (e.g., CI), ii) result of something unrelated to MS but in a population where CI is common, or iii) result of pathology simultaneously producing changes in mood and cognition – undermines the perspective of depression functioning as a confound to the accuracy of cognitive PROs (e.g., 94). However, there are credible psychological mechanisms of depression that complicate the use of cognitive PROs in people with MS. Namely, people with depression have a tendency to process information in a negative manner (143,151). This may result in a general devaluation of the self (151), thereby manifesting specifically in a negative appraisal of one's cognitive abilities, what has been referred to as "mood-congruent cognitive bias", or "cognitive impairment bias" (93,142,143).

5.2.2 Fatigue as Symptom of Cognitive Decline

Current findings indicated moderate-large, non-significant correlations between fatigue and cognitive PROs/insight in the MS group and thereby comport with previously reported

relationship effect sizes between cognitive PROs and fatigue in MS (93,95). The relationship between PROs of cognition and fatigue in people with MS may be due to overlapping neurological bases of the constructs assessed by these measures. The following paragraphs will attempt to articulate this in greater detail.

Fatigue is regarded as the resultant state of a disproportionate estimation of the energetic cost (i.e., effort) of an action (e.g., mentation) coupled with a relative devaluation of the intended outcome of said action (152,153). Fatigue in neurological disorders has been proposed to be precipitated by pathology of the striato-thalamo-cortical fibers and/or structures such as the dorsolateral and ventromedial prefrontal cortex and the anterior cingulate cortex (153–155). These structures subserve cognition (156), the affective evaluation of potential goal states (157), and effort calculation (158). Hypoactivity and hyperactivity in these structures – likely due to reduced network capacity and compensatory responses to decreased network efficiency/capacity, respectively – have been documented to coincide with elevated MS fatigue (159,160).

Subjective cognitive decline (SCD) has been described as a stage in which an individual maintains demographically normal cognitive performance but perceives a reduction in their cognitive ability from a prior state (90). The coexistence of these features (i.e., perceived cognitive decrement despite unimpaired performance) is theorized to arise from an individual's resilience to subtle pathology – making functional changes undetectable via testing, yet experienced as difficulty in daily cognitive tasks (90). Presumably, this resilience in SCD can be explained in terms of reserve mechanisms (discussed in *Section 1.2.2*), namely, reductions in network efficiency in individuals of high premorbid efficiency and/or hyperactivity to compensate for reduced network efficiency and/or capacity. According to the referenced conceptualization of fatigue (152,153), cognitive decline could implicate fatigue if there is a

greater demand for cognitive effort due to a need to compensate for network inefficiencies and/or reduced capacities. This extrapolation of the model (152–155) is seemingly compatible with the referenced neuroimaging literature on MS fatigue (159,160).

The present MS sample exhibited greater fatigue symptoms in addition to slowed IPS-related metrics (i.e., SDMT, Stroop-W, IPS, GC; moderate-large effects, non-statistically significant) and significant neurodegeneration (i.e., GCIPL thinning) relative to controls. Fatigue could arguably be taken as symptomatic evidence of compensation and/or dysfunctional cognitive effort-reward calculation in this sample (discussed below). Indeed, fatigue is associated with signs of structural/functional pathology in cognitively relevant structures such as the dorsolateral prefrontal cortex, ventromedial prefrontal cortex, anterior cingulate cortex, and the striatum (153,154,159,161).

The aforementioned neurocognitive model conceptualizes fatigue as a derivative of a disproportionate estimation of the energetic cost (i.e., effort) of an action (e.g., mentation) coupled with a relative devaluation of the intended outcome (i.e., reward) of said action (152). Accordingly, exaggerated estimations of energetic cost and/or abnormal devaluations of goal states might have contributed to the increased fatigue in the present sample. However, this conceptualization of fatigue would also suggest that within the compensated, normal range of cognitive performance – inefficient, energetically costly processing could elevate perceptions of mental effort in daily tasks, thereby making tasks more fatiguing. Given that the MS sample demonstrated evidence of neuroaxonal degeneration and IPS slowing, inefficient cognitive processing and increased energetic costs of daily tasks may account for some of the fatigue observed in this group. This interpretation partially contends with the view of fatigue as a non-cognitive influence on cognitive PROs that distorts the relationship between objective and

subjective cognition in people with MS (94). That being said, while theoretically grounded, estimations of energetic cost and goal state evaluation were not assessed in the current design and thus remain unsubstantiated, non-mutually exclusive sources of fatigue.

5.2.3 Interpreting the Neurocognitive Correlates of Cognitive PROs in an MS Sample with Compensated Cognitive Function

If the observed neuroaxonal degeneration in the MS sample with generally unimpaired cognition reflects a need to compensate, the moderate-large correlations between cognitive PROs and neuroaxonal degeneration add credibility to the stance that objective testing inadequately captures all cognitive symptoms (85). If the moderate-large group differences observed in neuroaxonal degeneration (pRNFL, GCIPL), cognition (Stroop-W, SDMT, GC, IPS), and fatigue are attributable to disease burden/progression, it may be tautologically reasoned that the MS group acquired neuroaxonal atrophy, cognitive dysfunction, and fatigue relative to a premorbid state. Thus, insofar as cognitive PROs coincided with neuroaxonal degeneration, fatigue, and reduced cognitive performance, Study 1 findings offer some limited support for the conclusion that cognitive PROs in people with MS reflect some of the neurocognitive changes they have undergone. This interpretation concords with the sentiment that cognitive PROs generally reflect an individual's comparison of their current cognitive status to their prior functioning (84,90). This interpretation of Study 1 findings similarly aligns with the observation that longitudinal changes in PRO_{GC} correlate more strongly with changes in GC, IPS, and visuospatial memory performance relative to how strongly PRO_{GC} correlates with performance cross-sectionally (162). This may explain why there was a relationship between PRO_{EF} and EF in controls, whereas in participants with MS of intact EF, PRO_{EF} reflected their experienced decrements (e.g., IPS), rather than what might be theoretically expected (EF).

5.3 On the Relationship between Cardiorespiratory Fitness and Patient-Reported Cognitive Functioning in People with Multiple Sclerosis

Study 2 analyses revealed that CRF was inversely correlated with cognitive PROs in participants with MS but was unrelated to cognitive PROs in controls. In particular, among the MS sample, higher CRF was associated with reports of more everyday cognitive dysfunction than would be anticipated from cognitive testing alone (i.e., "overestimation" of CI). Overestimations of GC/EF CI, however, corresponded with deficits in IPS, potentially indicating that these participants were sensitive to their cognitive decline. The relationship observed between cognitive PROs and CRF might thus be explained by higher CRF being associated with protective effects towards the neural substrates of insight (described below).

Although the neural correlates of insight in people with MS have not been studied, overlapping findings concerning such correlates in other populations offer some indication as to what structures generally underlie one's awareness of their deficits. Temporal lobe pathology can precipitate deficits in the ability to encode, consolidate and hence update information about the self, thereby yielding an outdated self-concept (163–165). To have insight of cognitive decline, one must be able to encode into memory that they have observed cognitive tasks become more difficult in their daily life and/or they have observed an increasing frequency of cognitive errors. The hippocampus is one structure likely mediating this process. For example, Hulst et al., (2014; 166) found that greater hippocampal volume was associated with elevated patient-reported GC dysfunction in people with MS. Conversely, in persons with preclinical AD (i.e., amnestic mild cognitive impairment; aMCI), temporal lobe atrophy has been documented to correspond with reduced insight of GC and language function (148). One potential explanation for Study 2 findings could thus be that participants with MS who had higher CRF overestimated CI as a

function of higher CRF being associated with enhanced hippocampal structure/function, thereby promoting awareness of their cognitive changes. Indeed, evidence suggests that within people with MS-related CI, those who undergo aerobic exercise training exhibit moderate-large (non-statistically significant) increases in memory performance and preserved hippocampal volume relative to non-exercise controls (50). A larger trial comparing two aerobic exercise interventions likewise found that people with MS in either condition exhibited improvements in memory (134).

Insight is likely subserved by more than just memory function. In people with MS, low insight of cognitive symptoms has been observed to be associated with low EF (112,113). Frontal lobe and/or parietal cortex pathology are thought to mediate difficulties in retrieving information stored about the self (163–165). In line with this notion, low insight for psychiatric symptoms in people with schizophrenia has been found to correlate with executive dysfunction and atrophy of the medial prefrontal cortex, anterior cingulate, striatum, and the temporal lobe (111). Similarly, reduced insight of memory decline among those with aMCI has been observed to be associated with atrophy of the anterior cingulate cortex and the pars triangularis of the inferior frontal gyrus (148). The relationship between insight and CRF in Study 2 might thus be further explained by higher CRF being associated with preserved/enhanced frontal structures and relatedly EF. There is evidence that aligns with this conclusion insofar as higher CRF has been found to be associated with preserved EF in people with MS (135,136). On the contrary, EF has been argued to be necessary but not sufficient for insight into one's clinical deficits (167). In particular, people with schizophrenia have been found to have low insight with low EF, low insight with preserved EF, and preserved insight with preserved EF, but not preserved insight with low EF (167).

Documented neural correlates of low insight for hemiplegia following a stroke – lesions in the temporal parietal junction, temporal pole, insula, ventral prefrontal cortex, cingulum, and striatum (168) – are similar to those reported of low insight in persons with preclinical AD (140,148) and schizophrenia (111). However, Pacella et al., (2019; 168) proposed that insight deficits of hemiplegia may result from reduced bottom-up attentional processing arising from structural disconnection of the ventral attention network and resultant inattention to salient errors in the form of no movement despite intended motor action. Pacella et al., (2019; 168) also proposed inferior frontal gyrus lesions and disconnection between the inferior frontal gyrus and premotor structures to mediate deficits in error monitoring, learning from errors (e.g., recognition of one's inability to perform a task), and consequently insight. While this mechanistic account has been proposed in the context of low insight for hemiplegia following stroke, it could likely also be applied in the context of cognitive decline in people with MS. For example, deficits in the ability to attend to salient features of cognitive errors in daily tasks could compromise insight of cognitive decline in individuals with MS.

Although the radiological features of reduced insight for MS-related CI have yet to be studied, it would be reasonable to expect that there is some consistency with the overlapping findings for low insight of CI, psychiatric symptoms, and motor deficits across distinct clinical populations (111,140,148,168). Considering this backdrop and that the current MS sample had intact EF, the correlation reported in Study 2 between CRF and insight might be potentially attributable to antecedent facilitators of CRF preserving the neural substrates of EF, bottom-up attentional processing, and/or memory (encoding, consolidation, and/or retrieval). Importantly, many of these outcomes were not measured in Study 2, and this interpretation of preliminary findings remains to be empirically supported by way of cognitive and radiological examination.

5.4 Clinical Significance

The degree of cognitive dysfunction patients experience in their daily lives may not be readily anticipated on the basis of cognitive testing alone; hence, cognitive PROs may aid clinicians in understanding the extent to which persons with MS are cognitively affected (85). Cognitive PROs may be used to facilitate the detection of subtle cognitive changes, prompt heightened clinical monitoring for further cognitive decline, and inform decisions regarding early implementation of cognitive assessment and/or rehabilitation. Importantly, cognitive PROs may also be used in combination with neuropsychological testing to grasp the degree of insight a patient has of their cognitive status. Insight of cognitive decline is likely important for one to be able to compensate to maintain daily functioning by way of strategy use (169). Of further concern, low insight in people with MS might implicate an inability to seek out clinical assessment of cognitive functioning. Evidence of low insight in a person with MS may thus justify monitoring for impairment via periodic use of screening batteries/tests and/or informant (e.g., a caregiver) input.

Study 1 findings indicate that cognitive PROs might reflect neurocognitive decrements in persons with MS. Indeed, cognitive PROs appeared to correlate with cognitive performance in a somewhat gradient fashion from less to more affected cognitive performance outcomes in the MS sample. Both PRO_{EF} and PRO_{GC} correlated with axonal and neuronal biomarkers in a gradient fashion from less to more affected; however, PRO_{EF} correlated more strongly with fatigue than did PRO_{GC}. Taken together, Study 1 findings provide preliminary support for the use of cognitive PROs as screening/monitoring tools for neuropsychological deficits and symptoms in people with MS.

In the current MS sample, overestimators of CI had lower neuroaxonal thickness than those accurately estimating or overestimating cognitive ability (i.e., underestimators of CI that did not have CI). This aligns with observations that SCD preceding MCI may coincide with greater amyloid beta accumulation (140). That being said, underestimation of CI in aMCI has been documented to be associated with increased amyloid beta accumulation and risk for conversion to AD (140,148). Taken together, assessing insight in persons with MS might be potentially informative of the risk of future cognitive decline as a function of where an individual performs on the continuum of MS-related cognitive decline. Overestimation of CI in the absence of clinically detectable CI might provide evidence of compensation for neuropathology and vulnerability to developing detectable CI. In contrast, if a patient appears unaware of cognitive changes, clinicians may consider the patient's need for a detailed neuropsychological assessment. Furthermore, persons with MS who underestimate CI may especially require cognitive rehabilitation, as such individuals may exhibit a reduced ability to strategically compensate for their CI in daily life (169).

Older adults implement cognitive strategies vis-à-vis their awareness of their cognitive decline (170). Therefore, insight is argued to enable individuals to compensate in daily life for reduced cognitive function (169). This notion is supported by findings that people with low insight of AD-related CI have reduced medication adherence, a greater rate of vehicular accidents, and increased caregiver burden (169). Reduced insight in people with MS has been observed to be associated with reductions in quality of life and performance of instrumental activities of daily living (171). The finding that CRF was associated with insight is clinically relevant to the extent that CRF may be targeted to potentially preserve insight. Should the maintenance of fitness have any role in the preservation of insight, patients with MS ought to be

proactively encouraged to engage in physical activity/exercise training in the hopes of preserving their cognitive insight. Research is needed, however, to clarify what mechanisms may account for this relationship, and more importantly, to identify exercise targets and training protocols that may be leveraged to preserve/rehabilitate insight in people with MS.

5.5 Gaps and Directions for Future Research

5.5.1 Consider the Effects of Cognitive Status on Insight

MS research has documented that patient reports of GC dysfunction coincide with greater thalamic and cortical atrophy (117), and counterintuitively, with preserved hippocampal volume (166). Neither of these studies measured insight, and only one (166) reported on their MS sample's cognitive performance, with deficits documented in memory, IPS, EF (working memory), and GC relative to controls. Research indicates that insight of deficits in neuropsychiatric/neurological populations depends on memory and EF (111,167,169,172). Nevertheless, the referred research (166) did not consider how the cognitive features of their MS sample could explain their findings. Namely, participants without memory CI would have presumably had more intact insight and less extensive hippocampal pathology relative to participants with insight deficits and more severe memory CI – as has been observed in AD research (140). Considering the influence of cognitive status on insight may thus facilitate the interpretation of the relationship between cognitive PROs and radiological outcomes. Prospective research examining this association should therefore interpret findings with respect to their sample's cognitive performance and/or insight.

5.5.2 Common Protocols to Measure Insight, Overestimation, and Underestimation

In MS literature, the measurement of insight and overestimation/underestimation of CI can vary considerably across studies. This ultimately limits the comparability of findings

between studies. For example, some studies assess insight using the degree of "concordance" (i.e., absolute discrepancy) between patient-reported cognitive function and ratings of cognition from an informant (e.g., a caregiver; 112,171). In collapsing negative and positive discrepancies into absolute values, however, this protocol is limited to treating under and overestimation of CI as a singular construct. Other researchers study positive and negative discrepancies between patient-reported and informant-reported cognition (114) or alternatively between patient-reported cognition and cognitive performance (86,103,173,174). Even in the context of creating discrepancy scores between cognitive PROs and objective cognitive performance metrics, different studies use different cognitive tests and PROs to create metrics of insight. To facilitate comparability between literature, consensus is needed on how to optimally measure insight. Research is thus necessary to understand which discrepancies between cognitive tests and PROs are the most clinically informative and feasible.

Studies on insight generally apply non-equivalent criteria for over and underestimation of CI; in turn, findings concerning either construct are made difficult to interpret between studies. For example, some studies that used discrepancy Z-score thresholds based on their MS sample distribution have used cut-offs as distinct as ±1 (174) and <0< (86). In comparison, other studies have operationalized overestimation and underestimation as discrepancy scores lower/higher than arbitrary extremes within the control group discrepancy score distribution (e.g., $25^{th}/75^{th}$ %iles, ±1.5 SD; 103,114). Beyond the use of non-equivalent working definitions, the approach of using cut-offs derived from small samples is inherently second-rate. In comparison to population-based criteria of overestimation/underestimation, sample-based cut-offs from distinct, small samples ultimately constrain the comparability between MS research and studies in other populations. Normative data on insight discrepancy scores and population-based cut-offs for

determining overestimation and underestimation are thus needed. Such cut-offs would ideally be determined by considering the clinical relevance of proposed cut-offs. Clinically meaningful definitions of overestimation and underestimation could be arrived at from findings on how different cut-offs predict ecological functioning (e.g., workplace performance, maintenance of social roles, caregiver burden, management of activities of daily living, treatment adherence). Neuro-QOL measures (175,176) present strong candidate PROs to be used in the construction of such a data set given that they are accessible, intended to be used for various neurological conditions, and have large normative data to derive PRO (GC and EF) T-scores (177).

5.5.3 Studying Associations between Patient-Reported Cognition, Neuropathology, and the Development of Cognitive Impairment

There may be subtle neurocognitive changes noticeable by individuals that are not yet detectable by cognitive performance metrics but might be detectable by sensitive measures of neurodegeneration in conjunction with cognitive PROs. Presumably, those with unimpaired test performance who “overestimate” CI and exhibit elevated neuropathology are sensitive to frequencies of cognitive errors in their daily life and/or experience cognitive tasks as being more fatiguing/effortful. An important question then is who among these persons has a heightened risk of transitioning into clinically detectable CI?

Understanding which neuropsychologically undetectable experiences of cognitive dysfunction in daily life closely align with MS pathology could help to identify which individuals are at the greatest risk of decompensating. Research is needed to elucidate what cognitive PROs, and types of overestimation (e.g., in memory, EF, GC, IPS) most strongly relate to disease biomarkers of brain structure and function. Identifying persons who will most likely develop clinically detectable CI may be further facilitated by considering patient experiences of

compensation (overestimation of CI) in conjunction with paraclinical markers indicating a need for such compensation. Namely, if the objective is to identify individuals at risk for clinically detectable CI, longitudinal research is necessary to understand which patient reports alone and/or in combination with biomarkers are prospectively most predictive of clinically detectable CI.

5.5.4 Explicate the Relationship Between Fitness and Insight and Patient-Reported Cognition

Study 2 findings offer limited evidence that CRF may be associated with preserved/ heightened insight of cognitive decline in people with MS. Importantly, no participants exhibited true underestimation of CI or low EF, something observed to coincide with reduced insight in people with MS (112,113). Research on the relationship between CRF and cognitive function suggests the two become more related among persons with MS-related CI (130). Consequently, an important gap for future research to address is how CRF and other components of fitness (e.g., body composition, muscular strength, balance) relate to insight in those with MS who possess insight deficits. Studying this gap is important considering the findings suggesting that AD-related insight deficits are associated with vehicular accidents, caregiver burden, and reduced medication adherence (169). In contrast, research indicates that higher insight in older adults enables strategic compensation for cognitive limitations in daily life (169,170), and people with MS with greater insight are more able to perform instrumental activities of daily living (171). Cross-sectional and longitudinal MS research addressing associations between components of fitness and insight may be useful in clarifying what types of exercise training or what components of physical activity more broadly may benefit insight. Experimental evidence is needed to address what effects physical activity/ exercise training can have on insight and its

cognitive underpinnings (e.g., EF and memory) in people with MS who underestimate, overestimate, and accurately estimate their cognitive function.

5.6 Limitations

The present thesis was limited in several regards. Briefly, the analyzed sample of people with MS was small and demographically homogeneous. There was a relatively narrow use of neuropsychological outcomes. Similarly, retinal biomarkers of neuroaxonal degeneration are limited surrogates of disease burden and replication is needed using more direct biomarkers (e.g., obtained from structural/functional MRI techniques). The use of CRF covered one dimension of fitness and further research is needed to both replicate Study 2 findings and determine if they generalize to other components of fitness (e.g., strength, body composition, balance). Furthermore, experimental/longitudinal research is needed to better understand how physical activity/exercise training might influence patient-reported cognition and insight in people with MS. Such research may inform how to effectively tailor behavioral interventions to circumvent CI early in the trajectory of MS-related cognitive decline. Because analyses herein were cross-sectional, causal conclusions regarding findings cannot be made.

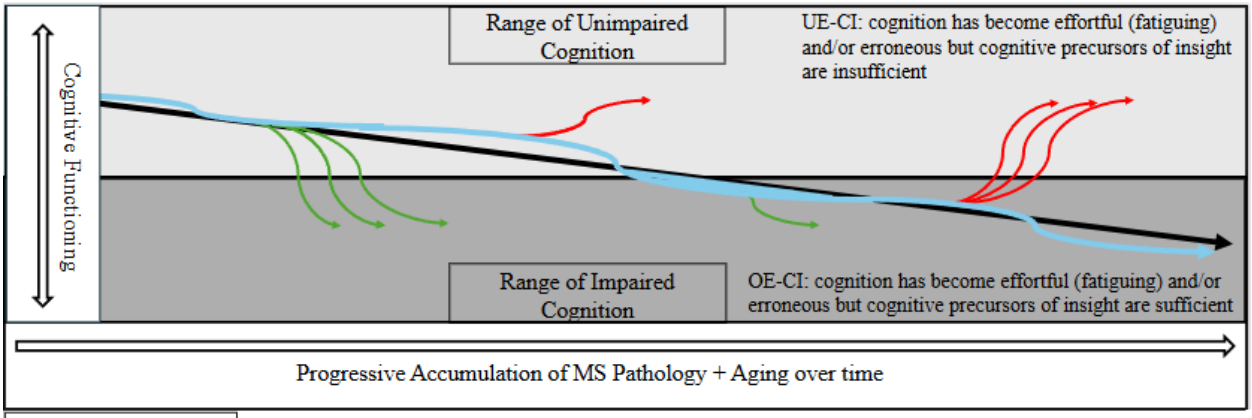
5.7 Conclusion

Standard neurological assessment may not capture the full extent of a patient's neurological dysfunction (85). Cognitive PROs offer feasible, patient-centered tools to ecologically gauge cognitive functioning. Extant MS literature quantifying the extent to which these outcomes relate to cognitive test performance and measures of pathology is limited. Likewise, there is a dearth of MS research on the protective effects of physical activity, exercise training, and fitness for patient-reported cognition.

Study 1 provided evidence that early in the course of MS cognitive decline, patient-reported cognition reflects some of the most affected, objective neuropsychological outcomes and that insight is unrelated to depression and fatigue – putative confounds of cognitive PROs (94,173). Study 2 provided evidence that higher CRF coincides with "overestimation" of CI. Importantly, the MS sample lacked true underestimators of CI – persons who dually overestimate cognitive ability and have CI. Relative to accurate estimators and "underestimators" of CI, those classified as overestimators of EF and/or GC CI exhibited unimpaired EF in combination with some of the most pronounced GCIPL thinning and lowest IPS performances. The inverse correlation between CRF and patient-reported cognition was accordingly interpreted as preliminary evidence that greater CRF is linked with heightened/preserved insight of cognitive changes occurring in the early stages of MS-related cognitive decline.

Longitudinal and experimental research is needed in larger and more diverse MS samples to both replicate and elaborate on findings herein. Current findings indicate cognitive PROs may have value as screening and monitoring tools for cognitive symptoms in people with MS. Furthermore, exercise training/ physical activity may be promising approaches to slow the decline of the neurocognitive underpinnings of insight in people with MS.

Figure 5.1 Model of Subjective Cognition in Relation to Cognitive Dysfunction and Decline



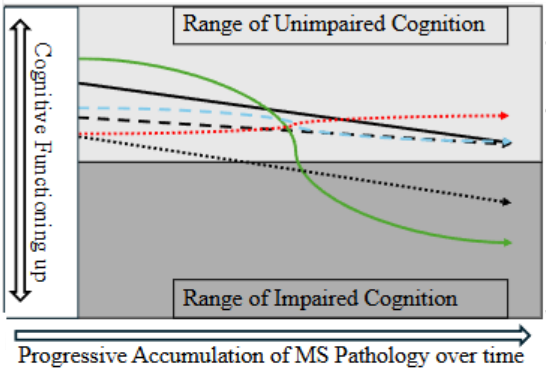
Legend
Cognitive Performance ↘
Perceived Cognition
- OE-CI
- UE-CI
- Acc-CI

The presented model assumes accurate estimations (blue arrow) to be standard. The model attempts to depict that the onset of underestimation (red arrows) becomes more likely as cognition becomes increasingly dysfunctional. In contrast, the development of overestimation (green arrows) becomes more likely in those experiencing decline who retain higher cognitive precursors of insight (e.g., memory, executive function).

Note. Increasing/decreasing frequency of red and green arrows attempt to depict the likelihood of overestimation/underestimation as a function of cognitive decline experienced and overall level of objective function (black arrow).

Note. OE-CI=overestimation of cognitive impairment, UE-CI=underestimation of cognitive impairment, Acc-CI=accurate estimation of cognitive impairment, MS= multiple sclerosis.

Figure 5.2 Depiction of the Potential Influence of Premorbid Function and Cognitive Reserve on Subjective Cognition



Course	Graphical Representation	Objective Cognition	Insight Classification
A		High Average – Average	Acc-OE
B		Average – Average	Acc-Acc
C		Low Average – Impaired	Acc-UE

Individuals with higher reserve may have proclivities toward overestimation. This is exemplified by two individuals (A and B) of indistinguishable cognitive ability with different pre-MS function (higher vs. lower; A vs. B). In comparison to person B, person A, who experienced larger reductions cognition, network efficiency/capacity, and who is presumably more reliant on compensation (reserve mechanism), may be especially likely to perceive cogitation as being effortful (and thereby fatiguing) or erroneous relative to their previous ability. In turn, person A may more likely be classified as an over-estimator of cognitive impairment.

Low premorbid function/reserve may predispose individuals to underestimate cognitive impairments. This is exemplified by two individuals (A and C) experiencing similar degrees of decline with one individual (C) more quickly reaching impairment because they declined from a lower level of function/reserve. In turn, person C more quickly exhausts their cognitive precursors of insight and thereby underestimates their impairment.

Note. OE=overestimates cognitive impairment, Acc=accurately estimates cognitive impairment, UE=underestimates cognitive impairment, MS=multiple sclerosis.

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Appendix - 1 University of Ottawa REB Approval Letter

07/03/2024

Université d'Ottawa
Bureau d'éthique et d'intégrité de la recherche

University of Ottawa
Office of Research Ethics and Integrity

CERTIFICAT D'APPROBATION ÉTHIQUE | CERTIFICATE OF ETHICS APPROVAL

Numéro du dossier / Ethics File Number	H-11-21-7484
Titre du projet / Project Title	Synergetic effects of Aerobic Exercise Paired with Non-Invasive Brain Stimulation to Prime Neuroplasticity in Multiple Sclerosis
Type de projet / Project Type	Recherche postdoctorale / Postdoctoral research project
Statut du projet / Project Status	Renouvelé / Renewed
Date d'approbation (jj/mm/aaaa) / Approval Date (dd/mm/yyyy)	15/12/2021
Date d'expiration (jj/mm/aaaa) / Expiry Date (dd/mm/yyyy)	14/12/2024

Équipe de recherche / Research Team

Chercheur / Researcher	Affiliation	Role
Arthur CHAVES	École interdisciplinaire des sciences de la santé / Interdisciplinary School of Health Sciences	Chercheur Principal / Principal Investigator
Lara PILUTTI	École interdisciplinaire des sciences de la santé / Interdisciplinary School of Health Sciences	Superviseur / Supervisor
Shida POURLOTFI	École interdisciplinaire des sciences de la santé / Interdisciplinary School of Health Sciences	Assistant de recherche / Research Assistant
Julia LUDGATE	École interdisciplinaire des sciences de la santé / Interdisciplinary School of Health Sciences	Étudiant-chercheur / Student-researcher
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Conditions spéciales ou commentaires / Special conditions or comments

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07/03/2024

Université d'Ottawa

Bureau d'éthique et d'intégrité de la recherche

University of Ottawa

Office of Research Ethics and Integrity

Le Comité d'éthique de la recherche (CÉR) de l'Université d'Ottawa, opérant conformément à l'*Énoncé de politique des Trois conseils* (2014) et toutes autres lois et tous règlements applicables, a examiné et approuvé la demande d'éthique du projet de recherche ci-nommé.

L'approbation est valide pour la durée indiquée plus haut et est sujette aux conditions énumérées dans la section intitulée "Conditions Spéciales ou Commentaires". Le formulaire « Renouvellement ou Fermeture de Projet » doit être complété quatre semaines avant la date d'échéance indiquée ci-haut afin de demander un renouvellement de cette approbation éthique ou afin de fermer le dossier.

Toutes modifications apportées au projet doivent être approuvées par le CÉR avant leur mise en place, sauf si le participant doit être retiré en raison d'un danger immédiat ou s'il s'agit d'un changement ayant trait à des éléments administratifs ou logistiques du projet. Les chercheurs doivent aviser le CÉR dans les plus brefs délais de tout changement pouvant augmenter le niveau de risque aux participants ou pouvant affecter considérablement le déroulement du projet, rapporter tout évènement imprévu ou indésirable et soumettre toute nouvelle information pouvant nuire à la conduite du projet ou à la sécurité des participants.

The University of Ottawa Research Ethics Board, which operates in accordance with the *Tri-Council Policy Statement* (2014) and other applicable laws and regulations, has examined and approved the ethics application for the above-named research project.

Ethics approval is valid for the period indicated above and is subject to the conditions listed in the section entitled "Special Conditions or Comments". The "Renewal/Project Closure" form must be completedfour weeks before the above-referenced expiry date to request a renewal of this ethics approval or closure of the file.

Any changes made to the project must be approved by the REB before being implemented, except when necessary to remove participants from immediate endangerment or when the modification(s) only pertain to administrative or logistical components of the project. Investigators must also promptly alert the REB of any changes that increase the risk to participant(s), any changes that considerably affect the conduct of the project, all unanticipated and harmful events that occur, and new information that may negatively affect the conduct of the project or the safety of the participant(s).

Coordonateur / COORDINATOR
Coordonnateur de l'éthique / Ethics Coordinator
Pour/For **Daniel LAGAREC** Président(e) du/ Chair of the **Comité d'éthique de la recherche en sciences de la santé et sciences / Health Sciences and Sciences Research Ethics Board**

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