COGNITIVE CORRELATES OF FATIGUE IN PEDIATRIC-ONSET MULTIPLE SCLEROSIS

TRACY LAUREN FABRI

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Abstract

Fatigue is common in pediatric-onset multiple sclerosis (POMS), yet causal factors and correlates of fatigue are poorly understood in this population. A systematic review of fatigue and cognition was conducted in Chapter 2. The available evidence confirms that fatigue is a common symptom in POMS with rates in samples varying from 9-76% and symptoms typically severe and functionally impairing for POMS patients. The relationship between parent- and self-reported fatigue and cognitive performance is not consistently found in the literature, though higher levels of fatigue tend to associate with performance on measures of sustained visual attention and task switching.

In Chapter 3, we investigated associations between cognitive and clinical features of POMS, namely objective fatigability, and subjective fatigue. Fatigability was operationalized as response time variability on a brief version of the Continuous Performance Test (CPT). We found that there is a significantly greater probability of parents and participants endorsing severe fatigue in POMS relative to age- and sex-matched healthy controls (HCs). We also identified that POMS were less accurate and more variable in their performance on the CPT relative to HCs. We did not however observe the expected associations between performance-related fatigability on the CPT and severe levels of parent- and self-reported fatigue. Finally, diffusion tensor imaging was used to explore neural correlates of fatigability. POMS participants demonstrated lower whole brain white matter integrity relative to HCs and while generally in the expected direction, white matter integrity was not significantly associated with fatigability on the CPT.

Until there is a cure for MS, it is essential that we continue to understand fatigue and its correlates in this population in order to develop targeted interventions, increase quality of life, and minimize the secondary impacts of fatigue.

Dedication

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List of Abbreviations

AD: Axial diffusivity
ADHD: Attention deficit hyperactivity disorder
ADS: Acquired demyelinating syndrome
AOMS: Adult-onset multiple sclerosis
APT: Attention Process Training
BRIEF: Behavior Rating Inventory of Executive Function
CBT: Cognitive behavioural therapy
CDI: Children's Depression Inventory
CFS: Chronic fatigue syndrome
CI: Cognitive impairment/cognitively impaired
CINAHL: Cumulative Index to Nursing and Allied Health Literature
CIS: Clinically isolated syndrome
CNS: Central nervous system
COV: Coefficient of variation
CPDDS: Canadian Pediatric Demyelinating Disease Study
CPT: Continuous Performance Test
CSF: Cerebrospinal fluid
DMN: Default Mode Network
DKEFS: Delis-Kaplan Executive Function System
DMT: Disease modifying therapy/therapies
DTI: Diffusion tensor imaging
EBV: Epstein-Barr virus
EDSS: Expanded Disability Status Scale
EEG: Electroencephalogram
EMBASE: Excerpta Medica Database
EMG: Electromyography
FA: Fractional anisotropy
FLAIR: Fluid-attenuated inversion recovery
FSS: Fatigue Severity Scale
HADS: Hospital Anxiety and Depression Scale
HC: Healthy control(s)
ICC: Intra-class correlation coefficient(s)
IIV: Intra-individual variability
ISD: Individual standard deviation
MD: Mean diffusivity
MOGAD: Myelin oligodendrocyte glycoprotein antibody disease
MPRAGE: Magnetization Prepared Rapid Gradient Echo
MRI: Magnetic resonance imaging
MS: Multiple sclerosis
NAWM: Normal appearing white matter
NMOSD: Neuromyelitis optica spectrum disorder
PASAT: Paced Auditory Serial Addition Test
PCNB: Penn Computerized Neurocognitive Battery
PedsQL-MFS: Pediatric Quality of Life Inventory™ Multidimensional Fatigue Scale

PICO: Population Intervention Comparison Outcome
PI-ED: Paediatric Index of Emotional Distress
POMS: Pediatric-onset multiple sclerosis
PPMS: Primary progressive multiple sclerosis
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCTs: Randomized control trials
RD: Radial diffusivity
RIS: Radiologically isolated syndrome
RRMS: Relapsing-remitting multiple sclerosis
SD: Standard deviation(s)
SDMT: Symbol Digit Modalities Test
SPMS: Secondary progressive multiple sclerosis
TMT: Trail Making Test
UVB: Ultraviolet B
WISC: Wechsler Intelligence Scale for Children
6MWT: 6 Minute Walk Test
25(OH)D: 25-hydroxyvitamin D

Chapter 1: Introduction and Background

Overview of Multiple Sclerosis

Originally termed *sclerose en plaques* in 1868 by Jean Martin Charcot, multiple sclerosis (MS) is a chronic, inflammatory, and demyelinating disease of the central nervous system (CNS) (Zalc, 2018). MS is described as an autoimmune attack on the brain, spinal cord, and optic nerve (Huang, Chen, & Zhang, 2017) that can sometimes occur in children and adolescents. There have been significant advances in imaging and an increased understanding of the genetics, immunology, and disease pathology of MS in the past decade. Lesion patterns unique to MS and other inflammatory and demyelinating conditions of the CNS have also been identified, helping to support differential diagnosis.

Both white and grey matter are vulnerable to the disease, even before symptom onset (Tremlett, Muger, & Makhani, 2022). Diffuse atrophy as well as injury to normal-appearing white matter (NAWM) are hallmark features of a progressive course (Huang, Chen, & Zhang, 2017). Disease presentation can differ from patient to patient due to individual variability in plaque location (He, Grossman, & Mannon, 2001; Huang, Chen, & Zhang, 2017; Love, 2006). In general, however, white matter lesions are often observed around the ventricles, in the optic nerves and tracts, the corpus callosum, cerebellar peduncles, subpial regions of the cerebral cortex, and long tracts in the spinal cord. Cortical and subcortical deep grey matter, most notably the thalamus, also show extensive pathology (i.e., lesions) and/or atrophy (Ontaneda et al., 2021). Studies in MS using both magnetic resonance imaging (MRI) and histopathological methodology demonstrate extensive involvement of the hippocampus among other brain structures due to demyelination and neuronal and synaptic loss (Ontaneda et al., 2021). Taken together, these structural brain changes in MS have been associated with reduced physical functioning, visual changes, cognitive deficits, emotional difficulties, and reduced quality of life including fatigue (Marrie et al., 2015; Nielsen et al., 2013).

Incidence and Prevalence

Canada reports one of the highest rates of MS internationally, with approximately 90,000 individuals (i.e., one in 250 people), living with the disease (Multiple Sclerosis Society of Canada, 2022). Most individuals diagnosed with MS are between 20 and 49 years of age, with a mean age of 43 years at time of diagnosis in Canada (Multiple Sclerosis Society of Canada, 2022). The disease also presents in childhood or adolescence in approximately two to 10 per cent of all MS cases (Banwell et al., 2007; Boiko et al., 2002; Ghezzi et al., 2017; Waldman et al., 2014). The worldwide incidence of pediatric-onset multiple sclerosis (POMS) is 0.05 to 2.85 per 100,000 children a year with a prevalnce of 0.7 to 26.9 per 100,000 children (Brola et al., 2022). POMS is diagnosed when the first clinical attack is experienced before 18 years of age (Chiaravalloti & DeLuca, 2008).

Most forms of MS disproportionately affect females. The exception is primary progressive MS (PPMS) which has a slight male preponderance (Ghezzi et al., 2017; Harbo, Gold & Tintoré, 2013; Huang, Chen, & Zhang, 2017). However, the sex ratio is almost equal (Yan et al., 2020) with some evidence of a higher proportion of male patients before puberty for patients with relapsing-remitting MS (RRMS) (Chabas, Strober, & Waubant, 2008). Hormonal changes appear to impact disease activity, evidenced by a reduction in relapses during pregnancy and an increased relapse risk in the post-partum period, typically up to three months post-partum (Bilbao et al., 2019; Vorobeychik et al., 2020). Additionally, milder progression of disease, namely no longitudinal change in mean diffusivity (MD), has been observed among males relative to females with RRMS (Hacohen, Ciccarelli, & Hemingway, 2017; Longoni et al., 2017), though this finding may be pediatric specific.

Pediatric-Onset Multiple Sclerosis (POMS)

It is believed that MS may be underdiagnosed in children and adolescents due to a failure to recognize the disease in this demographic (Chabas, Strober, & Waubant, 2008). In fact, retrospective reports highlight that for some patients diagnosed with MS in adulthood, neurological symptoms were recalled from late childhood or adolescence (Inaloo & Haghbin, 2013). While there are similarities in how the disease presents in adulthood and adolescence and the possibility that some individuals diagnosed in adulthood may truly have a pediatric-onset disease, adult-onset MS (AOMS) and POMS are considered distinct patient populations.

In young children with MS, disease onset is typically marked by a higher frequency of symptoms indicative of cerebellar or brainstem involvement (Chabas, Strober, & Waubant, 2008; Ghezzi et al., 2017). Children and adolescents with MS have more pronounced inflammation and experience a greater number of relapses, particularly near disease onset, relative to individuals with AOMS. While it may take longer to accrue disability and reach a secondary progressive course in POMS relative to AOMS, POMS patients are typically 10 years younger than their AOMS counterparts when they experience difficulties with ambulation. Elaborated on below, the effect of having the disease before complete formation of white matter pathways may explain the unique difficulties patients with POMS experience (Ghezzi et al., 2017).

POMS and the Developing Brain. Insult to a developing brain from chronic inflammation and demyelination is not limited to white matter as previously thought. In addition to interruptions to CNS myelinogenesis, POMS impedes the development of cortical and subcortical brain structures (Banwell & Anderson, 2005) and reduces age-expected brain volume growth (Aubert-Broche, et al., 2014; Gale et al., 2004). Moreover, total brain volume loss and regional grey matter atrophy have also been well documented in POMS. Some highly connected regions (e.g., the thalamus) show greater vulnerability relative to other regions (Aubert-Broche et al., 2011; Aubert-Broche et al., 2014; De Meo et al., 2019; Huang, Chen, & Zhang, 2017; Kerbrat et al., 2012; Mesaros, 2008; Till et al., 2011).

Imaging White Matter. Fractional anisotropy (FA) is the most widely used diffusion tensor imaging (DTI) metric, and is an indirect measure of white matter properties. Specifically, FA is a measurement of the unidirectionality of water molecules in tissue. Higher FA (i.e., values closer to one) suggests more organized nerve fibres. The degree of water diffusion is captured by mean diffusivity (MD), the sum of radial diffusivity (RD; diffusion of water perpendicular to the principal direction), and axial diffusivity (AD; water diffusion parallel to the principle direction). While all metrics are indirect measures of tissue properties, they are sensitive to the white matter changes that occur in neurological conditions such as MS (Soares et al., 2013).

In children and youth without neurodegenerative or neuroinflammatory disease, FA increases and MD decreases throughout development (Palmer et al., 2022). POMS however is associated with a failure to develop age-expected white matter and progressive loss of tissue integrity over time (Longoni et al., 2017).

While the corpus callosum is particularly sensitive to white matter pathology, reduced FA is also found in T2 hyperintense lesions that can occur in both cortical and subcortical structures (Akbar et al., 2016; Blaschek et al., 2013; Tillema et al., 2012; Vishwas et al., 2010). White matter alterations, namely decreased FA and increased MD have also been observed in the NAWM of POMS patients and is indicative of neurodegeneration. In an unpublished dissertation by De Somma in 2022 that was conducted on the same POMS cohort as this dissertation, statistically significant reductions in whole brain white matter integrity were observed. While longer disease duration is associated with lower FA in both AOMS and POMS (Blaschek et al., 2013), greater acute axonal damage has been observed in POMS relative to AOMS, especially considering the shorter disease duration (Alroughani & Boyko, 2018; Longoni et al., 2017; Pfeifenbring et al., 2015).

Clinical Course

The time of symptom onset or diagnosis does not necessarily mark the onset of the disease; there is evidence of an MS prodrome in AOMS and POMS patients that might span five to 10 years of more (Tremlett, Muger, & Makhani, 2022). An MS prodrome has been characterized by symptoms including fatigue, pain, headache/migraine, and/or mood related changes (i.e., depression and anxiety) (Makhani & Tremlett, 2021). At times, these nonspecific symptoms lead to neuroimaging. Radiologically isolated syndrome (RIS) can be diagnosed in patients and others (e.g., in a “healthy” research study participant with incidental lesions detected on MRI) (Makhani & Tremlett, 2021). RIS remains a putative biomarker of the prodrome and the relationship between RIS and an MS prodrome remains elusive, namely whether they are distinct, overlapping, and/or part of a continuum (Makhani & Tremlett, 2021). The exact prevalence of RIS is unknown.

There are four MS disease courses (also referred to as classifications or phenotypes). These include clinically isolated syndrome (CIS), RRMS, PPMS, and secondary progressive MS (SPMS). The MS subtypes were initially defined in 1996, and were refined in 2013 (Lublin et al., 2020). The label CIS is given when a patient's clinical presentation is characteristic of MS and there is radiological evidence of myelin loss in the CNS, though the diagnostic criteria for dissemination in time has not been met. CIS is not a diagnosis itself, but rather the initial clinical indicator of MS (National Multiple Sclerosis Society, 2021). In RRMS, neurological attacks are unpredictable, and followed by complete or partial recovery. RRMS is the most common disease course in both AOMS and POMS; RRMS almost exclusively accounts for POMS cases (i.e., 93-100% of diagnoses) (Boiko et al., 2002; Ghezzi et al., 2002; Yeh et al., 2009). SPMS initially presents as acute relapses and remissions before ongoing and irreversible neurological impairment and accrual of disability ensues (Huang, Chen, & Zhang, 2017). In PPMS, there is consistent deterioration of neurologic function due to diffuse grey and white matter atrophy and an absence of defined relapses. PPMS is less common and typically diagnosed at a later age (Huang, Chen, & Zhang, 2017; Multiple Sclerosis Society of Canada, 2022). The MS courses are depicted in Figure 1.

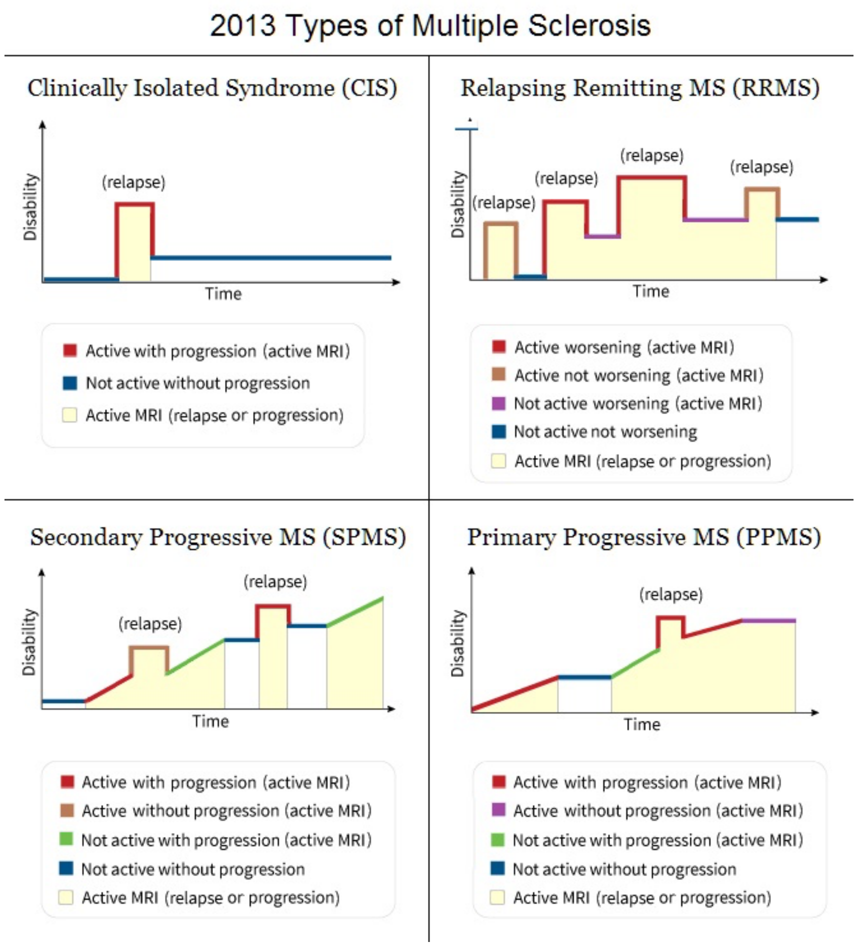

Figure 1. *Types of MS (My-MS, 2023)*

Etiology

Until recently, MS was thought to be the result of genetic and environmental factors, and their possible interaction with autoimmune pathophysiology. Viruses were also considered to play a role in the development of MS, though their contribution was uncertain. While the exact etiology of MS remains unclear (Huang, Chen, & Zhang, 2017; Love, 2006), recent research has revealed a strong epidemiologic correlation between Epstein-Barr virus (EBV) seropositivity and MS. A longitudinal analysis by Bjornevik and colleagues published in 2022 found that EBV seropositivity increased the risk of developing MS thirty-two times. These findings were not explained by any known MS risk factor. However, cigarette smoking and low vitamin D levels secondary to reduced sunlight exposure are environmental conditions that are still considered to mediate MS susceptibility (Wagner, Munger & Ascherio, 2004). In fact, higher latitude, specifically each 10-degree increase in distance from the equator, associated with a 10-month decrease in age of symptom onset in a 2016 study by Tao and colleagues. Moreover, in countries with the lowest ultraviolet B (UVB) levels (strongly linked to latitude), patients developed symptoms almost two years earlier in comparison to patients in countries with the highest UVB levels (Yan et al., 2020).

The novel finding that MS is exceedingly rare among individuals who are EBV-seronegative is a paradox; it contradicts the longstanding hygiene hypothesis (Ascherio & Munger, 2010). Whether EBV-seropositivity causes MS and how it may drive disease activity and progression remain uncertain. Researchers have argued against the idea of reverse causality, whereby immune dysregulation in the MS prodrome or preclinical phase increases the risk of being infected with EBV. The current view, at least in AOMS, is that MS appears to be a rare complication of EBV. While researchers are seeking to elucidate the role of EBV-seropositivity within the POMS population, published studies may be limited by the inclusion of individuals with CNS inflammatory demyelinating diseases other than MS (e.g., myelin oligodendrocyte glycoprotein antibody disease (MOGAD)). This is because lack of EBV exposure has been found to associate with a decreased risk of MOGAD (Gaudioso et al., 2023; Nourbakhsh et al., 2021).

What has been deduced thus far is that there is a larger proportion of EBV-seronegative pediatric patients thought to have MS, relative to adult MS samples. Specifically, whereas almost all AOMS patients have evidence of prior EBV exposure (Pakpoor et al., 2013), up to 15% of pediatric patients with a diagnosis of CIS or MS are EBV-seronegative, possibility indicating that an alternative diagnosis such as MOGAD may be more appropriate (Nourbakhsh et al., 2021). MRI and laboratory tests can be used to differentiate CNS disorders, described next.

Diagnosis and Differential Diagnosis

MS is often investigated following the sudden onset of neurological symptoms (e.g., weakness, numbness, tingling, balance and gait issues (ataxia), bladder or bowel dysfunction, or visual disturbance (Huang, Chen, & Zhang, 2017; The Children's Hospital of Philadelphia, 2014). Diagnostic standards have changed over time and MS diagnosis is currently made using the 2017 McDonald criteria (Polman et al., 2011). The 2010 McDonald criteria were updated in 2017 by the International Panel on Diagnosis of Multiple Sclerosis to better identify patients with a high likelihood of MS at CIS onset. MS is a diagnosis of exclusion that relies on clinical and paraclinical assessments including serum testing and analysis of cerebrospinal fluid (CSF). Imaging, particularly MRI helps to rule out other infections or types of inflammation (e.g., vasculitis) and confirm dissemination in space and time (Huang, Chen, & Zhang, 2017). Serology testing is used to identify seropositivity for antibodies against MOG and Aquaporin 4 (Yan et al., 2020), indicative of other conditions that may be MS mimics.

A body of literature supports the applicability of the McDonald criteria in children, especially those over the age of 11 (Polman et al., 2011). The International Pediatric Multiple Sclerosis Study Group defined the first diagnostic guidelines for POMS in 2007 (Krupp et al., 2007) and other updates have followed, most recently in 2017.

Disease and Symptom Management, Evolution, and Prevention

Several disease modifying therapies (DMTs) are available for use in MS. Diagnosis and prompt initiation of immunotherapy has improved greatly over the last decade and there are new and emerging second- and third-line treatments for MS that have undergone or are currently undergoing investigation in clinical trials. Ten to fifteen years ago, MS patients were either untreated or prescribed injectable beta-interferons or glatiramer acetate.

Today, DMTs are available in various routes including subcutaneous, intramuscular, infusion, and oral. While there is no cure for MS at present, DMTs may be used to prolong the interval between relapses and speed up recovery from attacks in RRMS. Some DMTs help slow disease progression in SPMS. Oral therapies are available for pediatric patients aged 10 or older with RRMS. Fingolimod, sold under the brand name Gilenya®, was approved by the Food and Drug Administration in 2018 for use in children with RRMS aged 10 and up (Chitnis et al., 2018). Natalizumab (Tysabri®) demonstrated comparable safety and efficacy in POMS and AOMS. Beyond its neurological/physical benefits, Natalizumab is associated with qualitative improvements in MS-related fatigue and cognition (Ghezzi et al., 2015; National Multiple Sclerosis Society, 2021; Penner et al., 2015). Amantadine and Modafinil are considered first-line agents in AOMS with positive results in double-blind placebo-controlled trials (Krupp, 2003).

In addition to DMTs, other interventions aimed at reducing relapse rate, fatigue, depression, and improving quality of life have been investigated in AOMS and POMS. As lower levels of 25-hydroxyvitamin D (25(OH)D) have been associated with a higher relapse rate in POMS, the effect of supplementation has been studied (Graves et al., 2016; Mowry et al., 2010). The level 1 evidence on supplementation with vitamin D for MS disease management is strong (Fernandez-Carbonell, Charvet, & Krupp, 2021). Further, there may be a role for vitamin D in the prevention of MS; children with higher levels of 25(OH)D at acute demyelinating syndrome onset demonstrated a lower risk of developing POMS in a 2011 study by Banwell and colleagues. While other alternative therapies like lipoic acid supplements, biotin (B_7), and cannabis may have utility in MS, there have not been any trials in POMS to date. This is due to the lack of safety data and concerns regarding adverse effects such as addiction, further brain volume loss, and potential cognitive consequences (Fernandez-Carbonell, Charvet, & Krupp, 2021). Finally, there is some evidence that vegetable intake is protective against relapse in POMS (Azary et al., 2018). With the knowledge of environmental risk factors, primary prevention of the disease necessitates population-level public health initiatives that at minimum, decrease exposure to recognized risk factors along with targeting those genetically predisposed to MS (Bebo et al., 2022).

In addition, several exercise interventions have been studied in randomized control trials (RCTs) in AOMS though no level 1 evidence studies have been carried out in POMS. This is despite the finding of lower levels of self-reported physical activity in this population relative to healthy youth and those with monophasic acute disseminated encephalomyelitis. Moreover, lower physical activity has been associated with greater disease burden (Grover et al., 2015; Grover et al., 2016). It is not known whether fatigue, depression, and/or other sequelae cause children with MS to be less active or vice versa. However, an association has been found between higher self-reported levels of physical activity and lower levels of sleep-rest and general fatigue (Grover et al., 2015).

Cognition in POMS

In addition to motor and visual changes, mood- and sleep-related disturbances, fatigue, and reduced quality of life, cognition is often affected in POMS (Cardoso, Olmo, & Fragoso, 2015; Till et al., 2011). Cognitive impairment (CI) is identified in approximately a third of POMS patients and is typically observed before pronounced physical disability (Amato et al., 2008; Amato et al., 2010; Banwell & Anderson, 2005; Ghezzi et al., 2017; Julian et al., 2013). This differs from AOMS, where physical symptoms often precede cognitive and psychosocial concerns, likely reflecting more spinal cord involvement in the adult population compared to youth with MS.

Memory, attention, executive functioning, and information-processing speed are often compromised, and deficits may appear early in the disease course (Till et al., 2011). Studies have demonstrated associations between younger age at disease onset, longer disease duration, and declining global and regional brain volume with cognitive deficits (Amato et al., 2008; Banwell & Anderson, 2005; MacAllister et al., 2005; Till et al., 2011). There is also a small body of research on the relationship between fatigue and cognition; it appears that fatigue may be related to performance on specific cognitive tasks and not others (Carroll et al., 2016). The findings of studies reporting the association or lack thereof between fatigue and cognition and a review of the quality of this research is detailed in Chapter 2.

Many cognitive abilities are immature at the time of initial CNS insult. Akin to brain volume which will be reviewed later, the observed gap in cognitive performance between youth with MS and healthy peers may reflect differences in developmental trajectories between these groups with the former failing to achieve age-expected cognitive gains; it may also indicate disease progression (Suppiej & Cainelli, 2014). Clinical and demographic factors, such as fluctuations in mood and fatigue, may also be associated with the variability observed in trajectories of cognitive performance in POMS (i.e., worsening, improved, or stable), though more research is needed to elucidate the relationship between these factors and cognitive changes (Canas, 2014; Julian et al., 2011).

Work by Amato et al., (2010) and MacAllister et al., (2007) demonstrated that cognitive deterioration occurs in patients with POMS. Findings from a prospective one-year longitudinal study by Till and colleagues (2013), found that POMS patients do not show the age-expected cognitive gains in several domains of functioning including attention, processing speed, language, executive functioning, visuospatial functioning, and memory. In the study by Till et al., (2013), lack of cognitive developmental gains was associated with MRI indicators of disease progression, namely increases in T1 and T2 weighted lesion volume. Further, in comparison to the healthy control group who showed significant gains on almost all neuropsychological measures in this study, the POMS group only improved between baseline and follow-up on four measures (i.e., Vocabulary, Similarities, and Block Design subtests from the Wechsler Abbreviated Scale of Intelligence, and the Letter Word Identification test from the Woodcock-Johnson Tests of Cognitive Abilities). Stability was observed on the other measures in this study which the authors postulate may have been due to either slight developmental gain or a smaller practice effect compared to the other measures administered.

An unpublished dissertation by Angela Canas (2014), documents similar findings. The author notes at approximately one-year follow-up, POMS participants demonstrated significant changes on cognitive tests. Further, Canas found that just under a third of their patient sample showed more declines than improvements, whereas just over half of POMS participants showed more improvements than they did declines. The remaining 15% of POMS participants had an equal number of improvements and declines. Performance declines were identified on auditory working memory, visual tracking and sustained visual attention, immediate verbal learning, and visual perception tasks, and performance improvements were identified on tests of motor-based processing speed, verbal fluency, and manual speed and dexterity. Higher levels of fatigue at baseline were found to predict a decrease in performance on Trails A.

In a 2014 study, Charvet and colleagues found that CI remained relatively stable in POMS over a mean of 1.65 years. These researchers hypothesized that the lack of decline in scores in their study relative to prior cohorts (e.g., Amato et al., 2010, 75% rate of decline across a mean interval of two years) may reflect characteristics of their sample (e.g., higher baseline IQ, older age at symptom onset) and methodology employed (i.e., less language assessment).

Research investigating whether DMTs protect or preserve cognitive function in POMS is in its infancy, with only two published studies to date (Johnen et al., 2019; Margoni et al., 2019). There are more studies of this nature in AOMS (e.g., Charvet et al., 2017). Findings of these studies appear promising for the preservation of cognitive function.

Cognitive neurorehabilitation for adults with MS, even delivered remotely via computer programs (e.g., RehaCom; Cerasa et al., 2013) has been shown to improve various aspects of cognition, namely attention, processing speed, memory, and executive functioning. There appears to be only one cognitive neurorehabilitation RCT that included POMS participants (Simone et al., 2018). This study also included a group of children and youth with attention deficit hyperactivity disorder (ADHD). Both groups were randomized to specific (i.e., Attention Process Training (APT)) or nonspecific home-based computerized training arms. Results indicate near transfer in the APT arm for both groups and greater far transfer for the POMS participants. There are also two non-RCT pilot studies (Hubacher et al., 2015; Till et al., 2019) that evaluated cognitive neurorehabilitation in POMS (Lin, Lin, & Hsu, 2020). In these studies, researchers evaluated home-based computerized programs for working memory. Outcomes included cognitive testing and indicators of program feasibility. Researchers found only modest effects of the intervention and far transfer was either not considered (Hubacher et al., 2015) or the evidence was unclear (Till et al., 2019). Correlates of the outcomes included disease burden, normalized brain volume, and general intelligence. In summary, there remains a dearth of knowledge regarding the most effective treatments for cognitive functioning in POMS. Continued research on the correlates of cognitive challenges in POMS may also inform future RCTs.

Fatigue in POMS

Fatigue is a common symptom in POMS with rates across samples varying greatly from 9-76%. In our prior work (e.g., Barlow-Krelina et al., 2021, Fabri et al., 2021, Fabri et al., 2022) we identified at a mean-group level, that parent- and self-reported fatigue were greater in POMS patients relative to controls. Some studies report that severe fatigue, which impacts school and recreational activities, occurs in approximately 40% of POMS patients (Carroll et al., 2016).

According to Findlay (2008) and a 2016 review by Carroll and colleagues, fatigue generally affects approximately 15-30% of the general adolescent population, indicating that the experience of fatigue is not limited to individuals with POMS or chronic illness. Severe fatigue is also reported by 20-33% of healthy teens and is more common among females (Sommer et al., 2022).

Cross-sectional, cohort, and qualitative studies on the clinical, cognitive, and physical correlates of fatigue were narratively synthesized in the 2016 review by Carroll and colleagues. They identified that fatigue shows a consistently strong association with depression, and that fatigue does not appear to associate with physical disability in POMS. The latter finding may be due to low levels of physical disability and lack of variability among POMS patients. As mentioned previously, the findings regarding fatigue and cognition are mixed, with the most consistent association found between higher levels of fatigue and poorer executive functioning (both performance-based and subjectively reported) and sustained attention. A few studies have found a relationship between fatigue and academic challenges in POMS. The latter may be due to more frequent absences from school and attentional difficulties. In closing, the 2016 review by Carroll and colleagues highlights that significant heterogeneity plagues the limited research concerning fatigue and its correlates in POMS.

The MS Council for Clinical Practice Guidelines defined fatigue in the late 1990s as “a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities” (Multiple Sclerosis Council for Clinical Practice Guidelines, 1998, p. 2). Despite this proposed definition, what “fatigue” truly is and how to best capture it is debated. In fact, differences in parent- and self-reported fatigue may be explained by the very subjective nature of fatigue and that it remains an ill-defined construct. Additionally, and perhaps consequently, fatigue has been understudied and a gold standard tool for assessing perceived (subjective) fatigue and performance (objective) cognitive fatigability is lacking (Braley & Chervin, 2010). Indeed, these issues have been cited as barriers to evaluating potential interventions to manage this symptom/experience in POMS (Fernandez-Carbonell, Charvet, & Krupp, 2021; Kluger, Krupp, & Enoka, 2013; Storm Van's Gravesande et al., 2019). As such, we must continue to strive to understand fatigue and its correlates, particularly in a heterogeneous clinical population such as MS. For example, if fatigue is explained by depression, interventions targeting mood would be appropriate, however, if fatigue is more strongly associated with white matter injury, a different approach to intervention may be warranted.

One RCT in AOMS considered whether cognitive behavioural therapy (CBT) was effective as a treatment for MS fatigue relative to relaxation therapy (van Kessel et al., 2008). Researchers of this study found that both CBT and relaxation therapy were effective, and while fatigue was equivalent to the control group six months after the intervention, greater benefits were observed in the patients who received CBT versus relaxation therapy. Other RCTs in AOMS have not seen benefits at follow-up (van den Akker et al., 2017).

Subjective Fatigue. In POMS research, fatigue is often measured subjectively using self- and proxy-reported questionnaires including the Pediatric Quality of Life Inventory™ Multidimensional Fatigue Scale (PedsQL-MFS: Varni et al., 2002). The PedsQL-MFS (Varni et al., 2002) breaks fatigue into general (e.g., feeling too tired to do things that you want to do), sleep-rest (e.g., sleeping a lot), and cognitive (e.g., difficulty thinking quickly) fatigue. It provides a total fatigue score that encompasses ratings on all 18 items for both proxy- and self-reports. The PedsQL-MFS (Varni et al., 2002) asks how much of a problem each item has been *in the past month.* Each item is rated on a five-point Likert scale ranging from zero representing "almost never" to four representing "almost always." Items are reverse scored such that higher scores represent better quality of life and less fatigue. The PedsQL-MFS (Varni et al., 2002) has demonstrated acceptable validity, internal consistency reliability (across various pediatric medical populations), test-retest reliability, and interrater reliability (Canas, 2014; Varni, Burwinkle, & Szer, 2004). Internal consistency reliability was .95 for the child/self-report total score and parent-reports respectively using Cronbach's alpha. The reliability of each subscale was also considered excellent, ranging from .88-.96. The construct validity of the PedsQL-MFS (Varni et al., 2002) was confirmed through medium to large intercorrelations with dimensions of generic and rheumatology-specific health-related quality of life.

While other fatigue measures have been used in POMS, these measures have not been validated for younger MS patients and may not be sensitive enough to detect associations with clinical and cognitive outcomes (Amato et al., 2014). In AOMS, the Fatigue Severity Scale (FSS; Krupp et al., 1989) is often used. The FSS (Krupp et al., 1989) has an internal consistency of .88 and a test–retest reliability of .84 using Cronbach's alpha. When the psychometric properties were assessed, scores on the FSS (Krupp et al., 1989) were significantly higher for individuals with MS and systemic lupus erythematosus compared to healthy controls and correlated with other measures of fatigue.

The Modified Fatigue Impact Scale (Braley & Chervin, 2010) was suggested for use in AOMS by the Multiple Sclerosis Council for clinical practice guidelines. It was modified from the original 40-item Fatigue Impact Scale (Fisk et al., 1994). These scales conceptualize fatigue as a predominantly physical symptom (e.g., "Fatigue is among my most disabling symptoms"; "Fatigue interferes with my physical functioning"). The Chalder Fatigue Scale (Chalder et al., 1993) has also been used in MS research in both pediatric and adult samples, though its validity and reliability have not been established in MS.

Fatigability. Objective fatigue is often measured using tasks where physical or motor output can be assessed over time. Despite the confound of physical disability particularly in AOMS, studies of motor and cognitive fatigability, also called performance fatigability, are emerging in MS (Agyemang, Berard, & Walker, 2021; Aldughmi, Bruce, & Siengsukon, 2017; Motta et al., 2016; Wojtowicz, Berrigan, & Fisk, 2012).

Motor fatigability has been measured using the 6 Minute Walk Test (6MWT), evaluating peak force before and after performing an exercise, and monitoring muscle contractions using electromyography (EMG)) during tasks requiring power output (Kluger, Krupp, & Enoka, 2013). In one study for example, Theunissen et al., (2023) reported changes in muscle fatigue in people with MS performing the 6MWT, quantified using bilateral EMG; patients also endorsed increases in perceived exertion (Theunissen et al., 2023).

Cognitive fatigability has been defined as an observable change in task performance and be assessed using within-subject response time variability, (also called intra-individual variability (IIV) or inconsistency) on cognitively effortful sustained attention tasks (e.g., Continuous Performance Test (CPT), Computerized Test of Information Processing) (Morrow, Rosehart, & Johnson, 2015; Walker, Lindsay-Brown, & Berard, 2019). It has also been measured by comparing an individual's performance before and after a "fatiguing" test is completed (Barrios et al., 2022). Typically, individual standard deviation (ISD) and the coefficient of variation (COV) are used as indices of IIV.

There are a few of studies that have probed the potential association between subjective fatigue and IIV (Aldughmi, Bruce, & Siengsukon, 2017; Bruce, Bruce, & Arnett, 2010). These studies found that MS patients demonstrated significantly greater response time variability compared to controls, and this was strongly associated with self-reported cognitive fatigue among patients with RRMS and SPMS. However, in the study by Aldughmi, Bruce, & Siengsukon (2017), which included 52 adults with MS, only the attentional task (i.e., CPT) (of the three performance fatigability measures – CPT, grip strength, 6MWT) significantly associated with the patients' subjective report of fatigue, specifically the physical and cognitive domain scores. The authors postulate that the long and monotonous nature of the CPT (i.e., continuously tapping for almost 15 minutes) relative to the other tests contributed to the association. State levels of fatigue were also higher after completing the cognitive fatigability tasks.

Subjective Fatigue and Fatigability: Conceptual Frameworks and Taxonomies. Kluger, Krupp, & Enoka (2013) highlighted the importance of defining fatigue and differentiating primary fatigue from secondary causes. In their proposal for a unified taxonomy of fatigue, they indicate perceptions of fatigue and performance fatigability as two major contributory factors . Given the prevalence of fatigue in the general population, they note the importance of determining criteria and appropriate measurement for assessing clinically significant fatigue and fatigability in neurological populations. Their taxonomy was based on answering the following questions in both research and clinical settings: 1) Is this fatigue or a related phenomenon? 2) Is the focus perception or performance? 3) Is it clinically significant? 4) Are there identifiable causal factors? 5) Is there a particular domain of task performance affected?

The first question about fatigue-related phenomena has great importance for the study of fatigue in MS given the prevalence of sleep and mood disorders that can overlap with fatigue symptoms. As such, they advocate that fatigue should be differentiated from related phenomena by covarying mood and sleepiness for example.

Differentiating perception of fatigue from performance fatigability is also highlighted given that they may be independent. Additionally, because fatigue and fatigability also occur in healthy individuals, there is a need to operationalize what constitutes “clinically significant.”

According to their model shown in Figure 2, underlying factors of perceived fatigue include homeostatic and psychological factors, whereas peripheral and central factors are associated with fatigability.

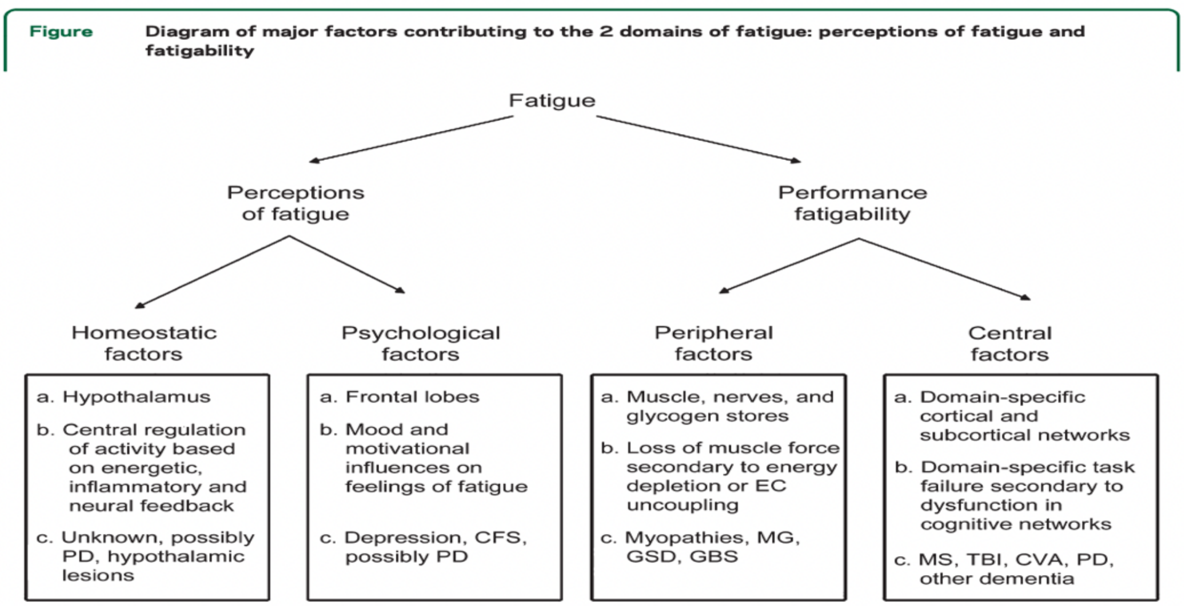

Figure 2. *Kluger, Krupp, & Enoka (2013)*

Homeostatic factors can include metabolic features that may induce the sensation of muscle fatigue (e.g., depletion of muscle glycogen, phosphocreatine, the accumulation of lactate), and increased brain temperature, inflammatory cytokines, changes in neurotransmitter levels, and regional pathology (for example to the hypothalamus) all within the CNS. Perceived effort, motivation, and mood are some of the psychological factors that may influence one's sense of personal fatigue. Peripheral factors and central factors are distinguished based on the organization of the nervous system.

The applicability of this taxonomy to measurement cannot be minimized. This is of particular importance given the heterogeneity in fatigue measurement, particularly assessing and quantifying subjective fatigue. Kluger, Krupp, & Enoka (2013) highlight the importance of using both a valid task and measure of fatigability, and note that choice of task can be made on the basis of current knowledge in the population of study and data derived from tasks in healthy individuals. The taxonomy falls short of identifying specific motor and cognitive tasks that can be used in clinical populations.

Figure 3 shows the 2019 model by Linnhoff and colleagues. This taxonomy adds to Kluger, Krupp, & Enoka's (2013) more general (i.e., applicable to any medical condition) model by honing in on subjective *cognitive fatigue* and objective *cognitive* fatigability, specifically in MS. Subjective fatigue can be defined as an ongoing feeling of exhaustion, whereas fatigability is objectively measured (e.g., performance decline during cognitive tasks). Linnhoff et al., (2019) further divide subjective fatigue into a trait and a state component, whereas fatigability is state-dependent and can be measured either behaviorally or with electrophysiological techniques. Accordingly, their proposed concept of cognitive fatigue implies that it can be studied both qualitatively (subjectively) and quantitatively (objectively).

According to Linnhoff et al., (2019), fatigability can be measured behaviourally by looking at changes in accuracy and reaction time. They also comment that mean response time or accuracy are not always associate with cognitive fatigue, and propose reaction time variability as a potentially more sensistive measure. Their taxonomy also speaks to electrophysiological assessment measures and interventions that are beyond the scope of this dissertation.

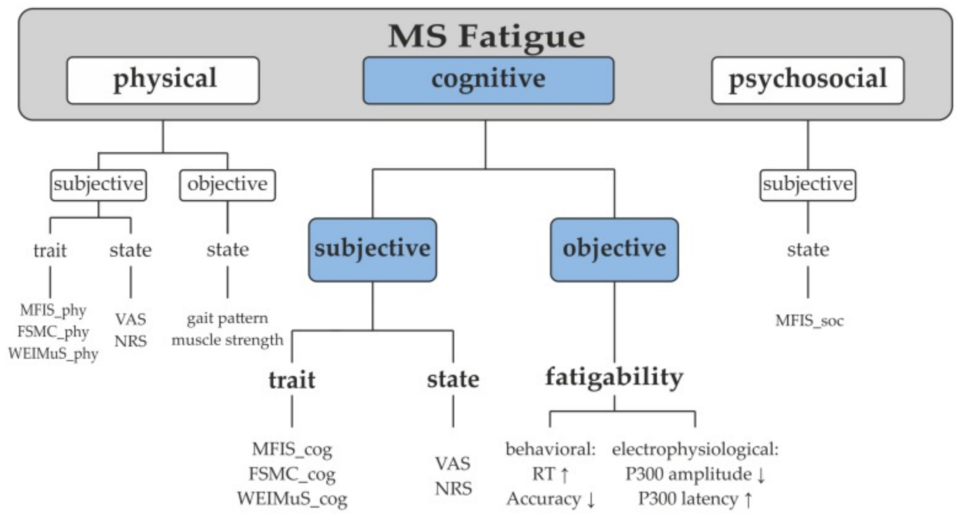

Figure 3. *Linnhoff et al., (2019)*

Correlates of Subjective Fatigue and Fatigability in Neurological Populations. The causal or pathological mechanisms of fatigue are largely unknown, possibly due in part to the lack of longitudinal studies. Fatigue may be secondary to disease markers such as inflammatory cytokines, mitochondrial dysfunction, neurodegeneration, changes in the neuroendocrine axis or neurotransmitter levels, and/or functional brain abnormalities (Ayache & Chalah, 2017; Field, 2021). It is also possible that chronic EBV activity or EBV reactivation in MS patients may be associated with increased inflammatory activity and this may contribute to increased feelings of fatigue (McElroy, 2023).

While causal factors remain largely elusive, researchers are beginning to reveal correlates of subjective fatigue and objective fatigability. The relationship between subjective fatigue and damage to white matter tracts in the prefrontal cortex in AOMS has been replicated across several studies (Bisecco et al., 2016; Pardini et al., 2010; Rocca et al., 2014). As well, one study in benign AOMS found that subjective report of fatigue and CI were associated with white matter microstructural damage and T2 lesion volume in the anterior thalamic tracts and in the corpus callosum (Bester et al., 2013). These findings imply that fatigue and CI may be related to microstructural damage and T2 lesion volume in frontal and white matter tracts that connect cortical and sub-cortical regions of the hemispheres.

Functional neuroimaging studies have shown a greater degree of IIV with increasing levels of functional disruption in bilateral middle frontal areas and thalamo-cortical circuits. Structurally, IIV has also been associated with decreased white matter volume (Bellgrove, Hester, & Garavan, 2004; Walhovd & Fjell, 2007).

Associations between white matter injury, subjective fatigue, and greater IIV have also been documented in healthy aging and clinical populations outside of MS, including traumatic brain injury, stroke, frontotemporal dementia, Parkinson's disease, mild CI, schizophrenia, and ADHD (Halliday et al., 2019; MacDonald, Li, & Bäckman, 2009; Sorg et al., 2021; Wiker et al., 2023; Wootton et al., 2023). As in MS, the precise mechanisms (e.g., impaired neuronal transmission, inflammation resulting in neurochemical changes/neurotransmitter disruption) underlying these brain-behaviour associations remain unclear.

In addition to neural and neuroimmune factors, clinical and behavioural correlates of fatigue include low mood and/or anxiety, sleep disorders, reduced physical activity, pain, iatrogenic sequelae, and potentially cognition (Braley & Chervin, 2010; Trojan et al., 2007).

Rationale and Study Overview

The available evidence in POMS suggests an association between fatigue and emotional difficulties, sleep disturbance, and reduced quality of life (Carroll et al., 2016). Identifying causal pathways between these sequelae and fatigue is complex. For example, whether these sequelae exacerbate the experience of fatigue, or how emotional difficulties manifest as a response to the feeling of fatigue is not understood in POMS. Even less is known about how the experience of feeling fatigued may impact cognitive function or vice versa (e.g., how fatigue induced by performing a sustained attention task may perpetuate self-reported symptoms of fatigue). This will be elaborated on across Chapters 2 and 3.

In Chapter 2, a systematic review of the literature examining the relationship between fatigue and cognition in POMS will be presented. This is an update to the previous 2016 systematic review (Carroll et al., 2016) of clinical and psychosocial factors including cognition and their relation to fatigue in POMS. We believed that contemporary studies may elucidate whether fatigue may be less problematic in POMS patients now, secondary to improvements in diagnosis and treatment. Relative to the prior review in this area by Carroll and colleagues (2016), we also took a rigorous approach to assessing the quality of each included study.

In a 2021 unpublished dissertation, Fields called on researchers to better understand the relationship between subjective report of fatigue and cognitive fatigability in healthy and POMS groups. As mentioned previously, clarifying relationships between fatigue, clinical characteristics, and disease pathology has the potential to inform intervention.

Motivated by and eager to build on the prior knowledge, IIV was investigated in Chapter 3 as a novel behavioural marker of fatigue (i.e., fatigability). Whole brain white matter was also examined as a possible neural correlate of fatigability. Whole brain DTI was chosen as we are investigating a novel outcome (i.e., IIV) in POMS, performance on the CPT largely relies on the integration of several pathways versus one specific pathway, and more broadly, we know that inefficient processing is subserved by white matter (Govindarajan et al., 2021).

This dissertation builds on the limited fatigue literature in POMS. It is important to preface this work by acknowledging the complexities of assessing fatigue, particularly in a condition such as POMS where there are great differences in disease-related factors (e.g., extent and location of CNS involvement) and developmental considerations.

Chapter 2: A Systematic Review of Associations Between Fatigue and Cognition in POMS

Abstract

Background and Objective

While fatigue has been associated with emotional difficulties, sleep disturbance, and reduced quality of life in pediatric-onset multiple sclerosis (POMS), information regarding the relationship between fatigue and cognitive challenges in this patient population is limited and mixed. The present study aimed to serve as an update to and expansion of a prior systematic review conducted in 2016 (Carroll et al., 2016).

Materials and Methods

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. Five electronic databases were searched (i.e., Medline, Excerpta Medica Database (EMBASE), PsycInfo, Web of Science, and Cumulative Index to Nursing and Allied Health Literature (CINAHL)) through July 2022. Reference lists of included studies were also hand-searched. Covidence was used to complete the screening, extraction, and quality assessment. The University of Adelaide JBI critical appraisal checklist for analytical cross-sectional studies was used to ensure the scientific rigor of each included study. Random effects meta-analyses were attempted and performed using R Statistical Software.

Results

A total of 15 studies which included empirical studies testing the association between fatigue and cognition were reviewed. Meta-analyses were limited by the inconsistencies in how fatigue and cognition were measured across the studies, which resulted in few studies that could be combined. As such, a narrative synthesis was ultimately conducted, with the quantitative analyses presented as supplemental. Eleven independent samples (n=559 patients with POMS)

were evaluated across the 15 included publications. Among the 13 publications and two dissertations that were reviewed, higher levels of fatigue were associated with poorer cognition in six, particularly on measures of executive functioning (both performance-based and subjectively reported) and attention; the remaining studies did not observe a statistically significant association.

Conclusions

Fatigue and cognition are not consistently associated in POMS. Some domains of cognition, namely executive functioning and attention, appear to be more sensitive to fatigue than others. Strengths and limitations of the reviewed studies are discussed; methodological heterogeneity across studies continues to plague this body of literature.

Introduction

Fatigue is among the most cited symptoms of multiple sclerosis (MS), especially adult-onset MS (AOMS). Fatigue has been strongly linked to impaired quality of life in AOMS, particularly in the domains of adaptive and occupational functioning; this is above and beyond depression and disability (Braley & Chervin, 2010; Krupp et al., 1988). The relationship between fatigue and cognition is not well established, in part because fatigue remains understudied in AOMS (Nunan-Saah, 2015). Even fewer studies have considered fatigue in individuals with POMS; among those that have, rates of fatigue vary widely with estimates ranging from 9 to 76% (Carroll et al., 2016). Fatigue may be understudied in MS because it is "invisible" and therefore difficult to measure objectively. The MS Council for Clinical Practice Guidelines defined fatigue in the late 1990s as "a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities" (Multiple Sclerosis Council for Clinical Practice Guidelines, 1998, p. 2). However, there is little agreement on what fatigue is and how to best quantify or measure it, particularly in a research context. Consequently, the causal factors and correlates of fatigue remain largely unknown.

Researchers and clinicians studying POMS typically rely on patients' self-reported fatigue. Sometimes a proxy-report is also requested from parents or caregivers, serving as collateral data on their child's fatigue. Higher levels of parent-reports of their child's fatigue have been found relative to self-reports (Carroll et al., 2016; Holland et al., 2014). While fatigue is reported by approximately 15-30% of adolescents without MS, fatigue is typically more severe and functionally impairing socially and academically in POMS. Severe fatigue is found in about 40% of patients (Carroll et al., 2016; Findlay et al., 2008).

The potential for new and emerging second- and third-line treatments for POMS to lessen fatigue remains unclear. In some studies, Natalizumab, has been associated with qualitative improvements in MS-related fatigue and cognition (Ghezzi et al., 2015; National Multiple Sclerosis Society, 2021; Penner et al., 2015) relative to first-line treatments such as injectable beta-interferons (Chitnis et al., 2018). The opposite was found in a study of AOMS whereby patients treated with Natalizumab had significantly higher fatigue scores compared to those receiving beta-interferons and glatiramer acetate. (Maier et al., 2023). Possible explanations for this finding include the significantly higher degree of disability observed among patients in the group being treated with Natalizumab. Fatigue is also a symptom of the “wearing off” phenomenon that has been described in patients using the drug (Bringeland et al., 2020).

Though Natalizumab has been available to pediatric patients under a surveillance plan as of March 2006 (see Yeh & Weinstock-Guttman, 2010 for more information), outside of research, many clinicians remain hesitant to prescribe it to patients under 18 years of age. Despite its apparent efficacy and safety, there remains a lack of randomized clinical trials in children and adolescents (Palavra et al., 2021).

The present study aimed to serve as an update to and expansion of a prior systematic review conducted in 2016 (Carroll et al., 2016). A meta-analysis was also planned to expand on the 2016 review by Carroll and colleagues which did not quantitatively synthesize the literature. The previous review found that fatigue may be related to performance on specific cognitive tasks and not others; it was broad in its scope and only briefly reviewed the literature on cognition in POMS as it relates to fatigue. Carroll and colleagues (2016) review included 14 papers encompassing 11 independent samples in their narrative synthesis. Among the 14 papers reviewed, only six assessed the relationship between fatigue and cognition.

Method

Inclusion and Exclusion Criteria

Table 1 summarizes the inclusion and exclusion criteria for studies in the systematic review.

Table 1. Inclusion and exclusion criteria for the systematic review

Inclusion Criteria	**Exclusion Criteria**
Empirical studies published between 2001 (following the publication of the first iteration of the McDonald criteria) and a statement that included patients had a confirmed clinical diagnosis of pediatric-onset multiple sclerosis using McDonald criteria or consensus definitions	Non-empirical (i.e., case studies, systematic reviews), general discussion, or theoretical papers
Measured fatigue	Studies not published in English
Measured clinical factors	Studies using mixed samples of age and/or demyelinating conditions where pediatric and/or multiple sclerosis-specific data could not be extracted
Measured cognition using a standardized assessment tool	Measured cognition using questionnaire
Examined the association between fatigue and clinical and cognitive outcomes either descriptively or by assessing bivariate or multivariate relationships	

Systematic review methodology and PRISMA guidelines were followed. Five electronic databases (i.e., Medline, EMBASE, PsycInfo, Web of Science and CINAHL) were searched for studies published between between December 2001 and July 2022. Search terms were specific to each database and can be found in Supplemental Document 1. Reference lists of included studies were also hand-searched. The Population Intervention Comparison Outcome (PICO; Richardson et al., 1995) statement framework was used to generate a research question and facilitate the search and is presented in Table 2.

Table 2. Search strategy and PICO statement

P	Pediatric-Onset Multiple Sclerosis
I	N/A
C	Other demyelinating disease and fatigue patient samples and healthy controls or a sample of POMS patients without fatigue
O	Fatigue and at least one cognitive or neuropsychological outcome

Covidence was used to complete the screening, extraction, and quality assessment. Two independent researchers (i.e., T.L.F, and/or S.D, and/or M.G) reviewed each paper included in the title and abstract screen and full text review. S.D and M.G completed the initial extraction and quality assessments. Conflicts at all stages were resolved by the lead author (T.L.F) who also extracted additional data for synthesis. The University of Adelaide JBI critical appraisal checklist for analytical cross-sectional studies (Moola et al., 2020) was used to broadly assess the scientific rigor of each study based on the following: clearly defined inclusion criteria, detailed description of study subjects and setting, valid and reliable exposure of the fatigue outcome, use of objective, standard criteria used to make the diagnosis of MS, identification of confounding factors and strategies to address them, valid and reliable measure of the cognitive outcome, and appropriate statistical analysis (Supplemental Document 2). For each item, studies were rated as either “Yes”, “No”, “Unclear”, or “Not applicable” and a subjective overall appraisal to “Include”, “Exclude”, or “Seek further info” was assigned.

Data Analysis and Synthesis

The data extraction template was slightly modified from the existing outline in Covidence (following PICO guidelines) for brevity. Additional details such as those pertaining to methods, are summarized in-text in the results section. Fatigue and cognitive data were first extracted from each study along with information on the association between fatigue and cognition (overviewed in Table 3; full extraction summary table available in Supplemental Document 3).

A meta-analysis of studies that reported correlations between fatigue and cognition was conducted using the *metafor* package in R Statistical Software (R Core Team, 2023). Studies available for inclusion were limited. As such, this was more exploratory, and a narrative synthesis was ultimately conducted. Comments on the association between fatigue and mental health outcomes were also made in Supplemental Document 3 for studies that explored this relationship.

Results

Database Search and Study Selection

1023 abstracts were identified through our initial search. We retained 118 articles for full text review. Fifty-one additional studies were identified from hand-searching reference lists of included studies, of which 24 were retained for full text review. A total of 15 papers were extracted and analyzed. The PRISMA flow diagram of the search process is presented as Figure 4.

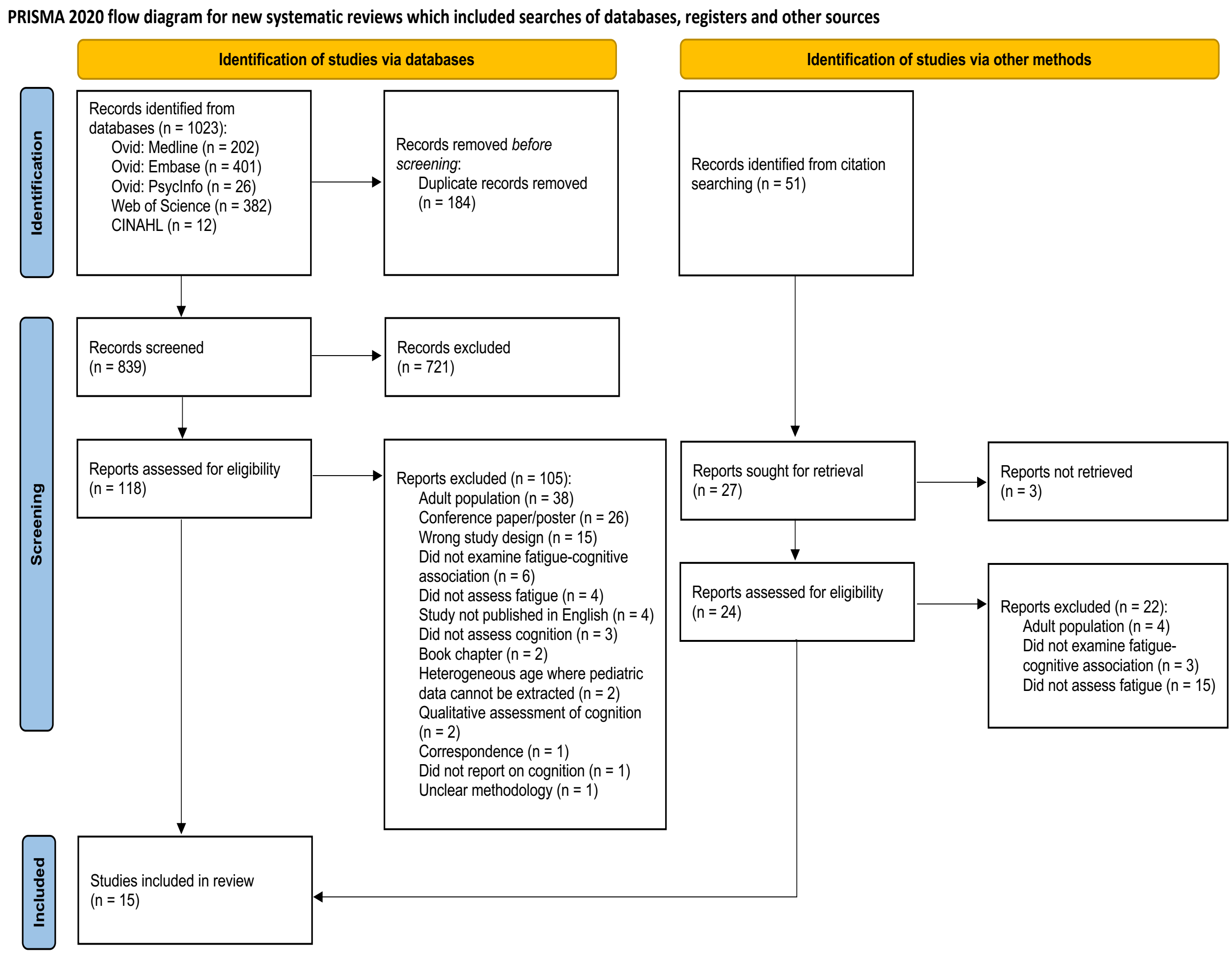

Figure 4. *PRISMA 2020 flow diagram*

Descriptive Characteristics of Included Studies

Four cohort studies (Amato et al., 2008; Amato et al., 2010; Amato et al., 2014; Canas, 2014), eight cross-sectional studies (Barlow-Krelina et al., 2021; Bigi 2017; Carroll et al., 2019; Charvet et al., 2016; Goretti et al., 2012; MacAllister et al., 2005; Nunan-Saah, 2015; Portaccio et al., 2020), and three retrospective studies (Fields, 2021; Holland et al., 2014; Nunan-Saah et al., 2017) were included and their data extracted. Four studies were from the same Italian patient cohort (i.e., Amato et al., 2008, Amato et al., 2010, Amato et al., 2014; Goretti et al., 2012). Both studies by Nunan-Saah (2015, 2017) used the same archival dataset, and there are likely overlapping participants in these studies. Of note, Canas (2014), Fields (2021), and Nunan-Saah (2015) are unpublished dissertations. Further, the 2017 publication by Nunan-Saah may be based on her 2015 dissertation. Taken together, 11 independent samples (n=559) were evaluated across 15 studies.

Studies were conducted in Italy, Canada and/or the United States of America, and the United Kingdom. Most patient samples were comprised of solely POMS patients, though Carroll et al., 2019 included a second clinical comparator group of pediatric patients with chronic fatigue syndrome, and Portaccio and colleagues (2020) included an AOMS group. Most of the sample (i.e., 77.1%) in Charvet et al., (2016) met criteria for relapsing-remitting MS (RRMS), whereas the remainder were labelled as clinically isolated syndrome (CIS). This study was retained in the review as the difference in cognitive functioning between the MS and CIS patients was not statistically significant. Furthermore, CIS is not a separate disease from MS. Rather, it is a timepoint when the confirmatory features of MS are not yet fully present (Dobson, Ramagopalan, & Giovannoni, 2012).

POMS sample sizes ranged from 20-111 and included patients between the ages of seven and 27 years. The Pediatric Quality of Life Inventory™ Multidimensional Fatigue Scale (PedsQL-MFS: Varni et al., 2002) was the most common measure of fatigue utilized in eight of the 15 included studies. "Mild" ratings on the PedsQL-MFS are defined as scores falling between one and two standard deviations (SDs) from the mean; "severe" ratings are defined as two or more SDs from the mean (MacAllister et al., 2009) in POMS. The Fatigue Severity Scale (FSS; Krupp et al., 1989) was used as the fatigue outcome in five studies. Dichotomous yes/no report was used in one study (MacAllister et al., 2005) and a ranking of "tiredness" was used for another (Bigi et al., 2017). This is detailed in Supplemental Document 3.

Quality of the Research

The JBI Checklist for Analytical Cross-Sectional Studies (Moola et al., 2020) was used to assess strengths and limitations of each study. We compared items across JBI checklists and found the checklist for cross-sectional studies to be suitable across study designs. All three researchers were independently involved in quality ratings and met to discuss any initial and rare discrepancies; after talking it through, there was always consensus. Despite the identified limitations described below, a consensus that all manuscripts/papers should be included was reached. This is depicted in Figure 5.

The 2005 study by MacAllister and colleagues was rated as "criteria not met" for exposure measurement as fatigue assessment was very crude. We also noted a lower quality of the cognitive measure under the outcome criterion, for studies that did not include the traditional Symbol Digit Modalities Test (SDMT) (i.e., Bigi et al., 2017; Carroll et al., 2019; Charvet et al., 2016; Holland et al., 2014; Nunan-Saah, 2015; Nunan-Saah et al., 2017). There lacks a universally accepted standard neuropsychological test battery for pediatric multiple sclerosis and the only 'gold standard' measure is the SDMT.

While the studies by Amato and colleagues (2008, 2010, 2014), Goretti et al., (2012) and Portaccio et al., (2020) commented on associations between fatigue and cognition, they failed to report a regression or correlation coefficient. Aligned with the JBI criteria, these studies were given a rating of "unclear" for statistical analysis. Email attempts were made to obtain these data from the authors, though lack of replies resulted in an inability to include these studies in our meta-analysis. The decision to solely include studies that reported a correlation coefficient in the meta-analysis was made to provide us with the most data for extraction; fewer studies reported statistical parameters from regression models and/or only reported an association between fatigue and select subtests (Bigi et al., 2017; Canas, 2014; Carroll et al., 2019; Holland et al., 2014; Nunan-Saah, 2015; Nunan-Saah et al., 2017). These latter studies are described in the narrative synthesis.

The dissertation by Fields (2021) was given a rating of "unclear/seek further info", as they looked at every potential association in supplemental analyses without control for multiple comparisons. Thus, there is a higher likelihood of a Type 1 error in this study. It is possible that other studies would have found associations between fatigue and cognition as well, though most studies took a more conservative analytical approach.

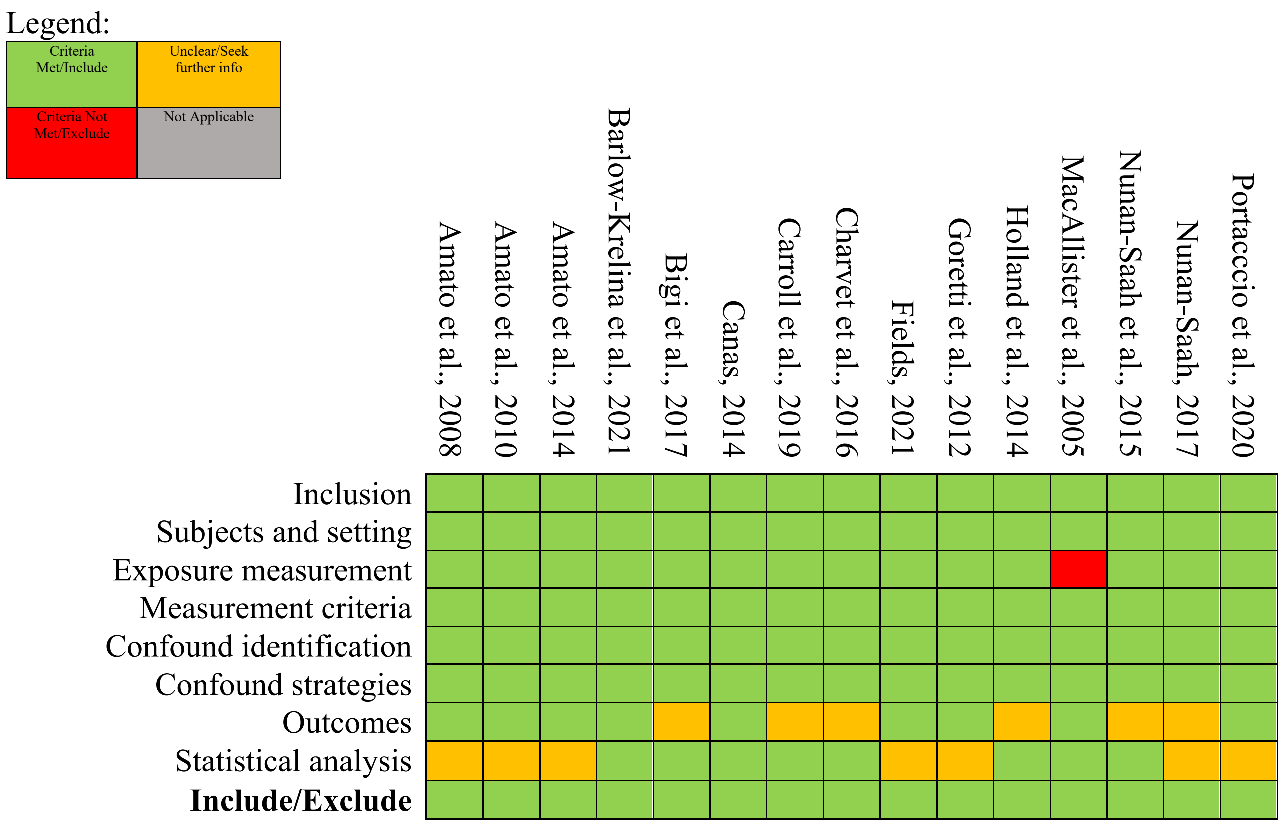

Figure 5. *Quality appraisal of included studies per JBI critical appraisal checklist*

Meta-Analysis

We aimed to establish an estimate of effect magnitude of the relationship between fatigue and cognition using random-effects meta-analysis. While a random-effects meta-analysis does not control for heterogeneity, it does provide a more conservative estimate of the overall effect size by incorporating the variability across studies.

Differing methodology across studies, namely the use of different fatigue measures, resulted in fatigue scores that could not be easily compared without adjustment. For example, higher scores on the FSS (Krupp et al., 1989) represent greater fatigue, whereas higher scores on the PedsQL-MFS (Varni et al., 2002) represent less fatigue and better quality of life. As such, adjustments were made so that scores in each study were consistent in the direction of fatigue severity.

Additionally, differences in the way the PedsQL-MFS (Varni et al., 2002) data were used across studies had the potential to complicate quantitative analyses. For example, Barlow-Krelina et al., (2021) applied the reverse scoring procedure for the PedsQL-MFS (Varni et al., 2002) in alignment with scoring directions. Here, higher scores on the PedsQL-MFS were indicative of less fatigue and that showed a small non-significant positive association with the cognitive composite. We emailed the author and supervisor of the 2021 dissertation by Fields after reading that they found a negative association between the Peds-QL-MFS (Varni et al., 2002) and cognitive outcomes. Their finding was explained as higher fatigue associating with greater cognitive challenges. Our correspondence clarified that raw scores were for their analyses (i.e., untransformed with the Likert scale ranging from 0 (never) to 4 (almost always) whereby a higher raw score would indicate greater fatigue). Consequently, we transformed the correlation coefficients (i.e., multiplied by -1) for the dissertation by Fields (2021), and the two studies (Charvet et al., 2016 and MacAllister et al., 2005) that utilized the FSS (Krupp et al., 1989; in this way, higher/positive scores represent less fatigue. Given the limited number of studies available for inclusion and that we combined different types of correlations (i.e., Spearman, Pearson, point biserial), results of our meta-analyses are reported in Supplement 4, and should be interpreted with some degree of caution.

Associations Between Fatigue, Cognition, and Clinical Characteristics

Results were mixed regarding the association between fatigue and cognition as well as fatigue and other clinical characteristics (e.g., disease duration, Expanded Disability Status Scale (EDSS) score, treatment with disease modifying therapies (DMTs), relapse rate, age at disease onset). A narrative synthesis of studies examining the association between fatigue and cognition is presented next, organized by studies that identified an association and those that did not.

Studies Identifying an Association Between Fatigue and Cognition. The study by Goretti et al., (2012) included fifty-seven POMS patients and 70 healthy controls (HCs) between the ages of 11 and 20 years. Significant cognitive impairment (CI) (i.e., failure on at least three tests) in this study was identified in 66.7% of patients, and mild CI (i.e., failure on two tests) in 9.5%. Cognitive performance worsened in 74.4% of cases at two-year follow-up. Rates of fatigue on the PedsQL-MFS (Varni et al., 2002) ranged from 9–14% on self-reports, and 23–39% on parent reports. Significant associations were found between self-reported fatigue and cognitive performance at the subtest level. Specifically, self-reported fatigue showed a trend towards being higher in patients with impaired problem-solving skills on the Tower of London Test (p=.05). Also, higher parent-reported fatigue was found for patients with impairment in verbal learning on the Selective Reminding Test – Long Term Storage (p=.03), processing speed on Trail Making Test B (TMT B) (p=.02), and executive function and verbal comprehension on the Token Test (p=.02).

A 2014 study by Holland and colleagues included 26 POMS patients (some still considered CIS but later confirmed to have MS) aged seven to 18 years. Impaired performance (i.e., <1.5 SD) on cognitive measures differed by test with up to 35% of the sample showing impairment on TMT B. Mean ratings of parent-reported general and total fatigue on the PedsQL-MFS (Varni et al., 2002) were severe whereas cognitive and sleep fatigue were considered mildly impaired using the criteria described in MacAllister et al. (2009). As in Goretti et al., (2012), parents more frequently reported significant concerns regarding fatigue (42%–58% reporting severe problems) relative to POMS patients (12%–31% reporting severe problems). Both parents and patients reported the least concerns for sleep-rest fatigue. A moderate to large correlation was observed between self-reported symptoms of general fatigue and reduced performance on TMT A (r=.48, p=.02) and TMT B (r=.49, p=.02). Similarly, parent-reported general fatigue was moderately correlated with performance on TMT B (r=.49, p=.03). The authors proposed that the motor component drives the association with fatigue versus the higher order cognitive skills that the TMT requires. This speculation was supported by a lack of a significant association between subjective fatigue and performance on a non-motor executive function task, the Letter Fluency subtest from the Delis-Kaplan Executive Function System (DKEFS; Delis, Kaplan, & Kramer, 2001).

Similar results were reported in an unpublished dissertation by Canas (2014). Participants included 20 POMS patients aged nine to 18 years at baseline. Significant CI (i.e., three or more scores at or below 1.5 SDs from the normative mean) at baseline was found in 45% of the sample. A focus of this study was identifying predictors of change in cognitive performance over time. The Reliable Change Index and Binomial Probability Distribution methods were used to assess changes in neurocognitive performance at the individual level. In this study, more participants (i.e., 55%) demonstrated improvements in cognitive performance than declines (30%). The remainder of participants (i.e., 15%) showed stable cognitive performance. Overall self-reported fatigue on the PedsQL-MFS (Varni et al., 2002) fell in the mildly elevated range defined by MacAllister et al., (2009) as between one and two SDs from the mean based on the Varni et al., (2002) normative sample. A decrease in performance on TMT A was most strongly associated with higher fatigue at baseline, though did not reach statistical significance due to low power (B=-0.37, $p<.10$).

A publication by Nunan-Saah and collaborators (2017) appears to be based on Nunan-Saah's 2015 dissertation given similarities in sample demographics, methods, and results. Both studies were reviewed and their quality appraised, though only findings of the publication are described herein. Their sample included sixty-five POMS patients between the ages of six and 18 years. Subjectively reported executive function challenges on the Behavior Rating Inventory of Executive Function (BRIEF; Gioia et al. 2000) showed a statistically significant association with subjective fatigue, whereas performance-based measures of executive functioning (i.e., DKEFS (Delis, Kaplan, & Kramer, 2001) Trail Making and Verbal Fluency) did not. Specifically, the PedsQL-MFS (Varni et al., 2002) total score on the self-report was associated with the BRIEF self-report using the Global Executive Composite (r=-.70, $p<.001$) and the BRIEF parent-report (r=-.50, $p<.01$). Likewise, the PedsQL-MFS parent-report associated with the BRIEF self-report (r=-.46, $p<.05$) and parent-report (r=-.58, $p<.01$). The authors postulate that the BRIEF may have greater ecological validity than performance-based measures of executive functioning, though it is also possible that the two self-report measures may be correlated as they are both driven by patient response bias (e.g., inflated responses across measures) (Shwartz et al., 2020).

An unpublished dissertation by Fields (2021), included retrospective data from 49 POMS participants with an average age of 14 years. Approximately 67% of the sample evidenced CI defined as performance at least one standard deviation below published means on any three or more cognitive tests across domains. Fatigue was measured with the PedsQL-MFS (Varni et al., 2002). Sixteen percent of the sample evidenced clinically significant self-reported total fatigue (i.e., raw score greater than 36), while 22% of the sample had clinically significant parent-reported total fatigue. Objective measures of working memory (Digit Span from the Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV; Wechsler, 2003)), processing speed (SDMT, WISC-IV Coding), and executive functioning (DKEFS Letter and Category Verbal Fluency, Trail Making Test – Switching; Delis, Kaplan, & Kramer, 2001) were used. No statistically significant relationships were found between parent- and self-reported total fatigue and the primary cognitive measures. Likewise, there were no group differences in fatigue ratings in cognitively impaired versus non-impaired patients. Moderate to strong relationships with the cognitive fatigue subscale score and DKEFS (Delis, Kaplan, & Kramer, 2001) Verbal Fluency Switching and Sorting, and response time on the Conners CPT, were observed in supplemental analyses (model parameters are not reported here for brevity but can be found in Field's dissertation). Notably, an alpha of .05 was used in the study and the author acknowledged the high potential of a Type I error due to the high number of comparisons. Though this study did report statistically significant associations between fatigue and cognition, the approach to analysis was quite liberal, therefore lowering the quality rating of this study.

Eleven independent samples were evaluated across 15 publications. In summary, six papers (including a publication and dissertation believed to have an overlapping sample; thus five of the 11 independent samples) identified some association between subjectively reported fatigue and cognition with correlations ranging from -.09 to .37; there were differences in whether a significant association was found between fatigue and performance-based neuropsychological tests versus standardized questionnaires. Next, we review the nine papers that did not identify a relationship between fatigue and cognition.

Studies Not Identifying Relationships Between Fatigue and Cognition. Thirty-seven POMS participants between the ages of eight and 17 contributed data to the study by MacAllister and colleagues (2005). Major CI (i.e., impaired performance on at least two cognitive tasks), was found in 35.1% of patients; fifty-nine percent were impaired on at least one cognitive measure. At one year follow-up, three patients who were cognitively impaired at baseline experienced further cognitive decline and five children who were not cognitively impaired at initial assessment were found to have declined at follow-up; these patients also experienced relapses between assessments. Fatigue (assessed by dichotomous yes/no self-report) was a concern for nearly half of the sample (i.e., 48.6%), but did not significantly correlate with the cognitive composite score ($r=-.23$, $p=.17$).

In the cohort studies by Amato and colleagues (2008, 2010, 2014) which utilized a comprehensive neuropsychological battery, criteria for significant CI (i.e., failing at least three tests) was found in 31% of patients at baseline and milder cognitive challenges (i.e., failing at least two tests) was found in 53% of patients. The original study cohort included 63 POMS participants. Of these participants, 56 participated in the first follow-up (2010), and 48 participants remained for the five-year follow-up in 2014. Significant and mild CI was found in 70% and 22% of cases respectively at two-year follow-up. Thirty eight percent of patients met criteria for significant CI at five-year follow-up with 10% experiencing milder CI. Whereas three quarters of patients showed declining cognitive performance between baseline and first follow-up, between first and second follow-up (i.e., years two and five), only 22.9% declined and 66.7% of patients appeared to improve, with 10.4% remaining stable. At baseline (as reported in the 2008 study), nine of 63 patients (14.29%) were classified as fatigued using a cut-off proposed for adults (i.e., a score of four on the FSS) (Krupp et al., 1989). Using this cut-off, 22% of patients were considered fatigued at first follow-up and 20% at second follow-up. The number of patients with fatigue was about equal when patients were grouped by CI status. These studies failed to detect an association between fatigue and cognition, potentially secondary to limitations with using the FSS (Krupp et al., 1989) in a pediatric sample and numerical results of the associations were not reported in text. The data were not received despite requests to connect with the author via email.

Charvet and colleagues (2016) considered the association between subjective fatigue and cognitive functioning using a composite z-score derived from performance on all neuropsychological tests. The study utilized the consensus battery of neuropsychological tests for use in the United States Network of Pediatric MS Centers. The battery assesses attention, executive functioning, and verbal and visual learning. While cognitive data were available for 120 POMS/CIS patients, only 66 participants completed self-report measures of fatigue severity. Approximately 37% of the sample demonstrated impaired cognitive performance (i.e., one or more standard deviations below published means on a third of cognitive tests). Mild to moderate fatigue was reported overall using the FSS (Krupp et al., 1989). No significant relationship was found between the composite cognitive z-score and self-reported fatigue severity ($r=.09$, $p=.48$).

In a Toronto-based study, Bigi and colleagues (2017) carried out a cross-sectional study including 27 POMS patients and 478 age- and sex-matched HCs. Participants with diagnosed anxiety and depression were excluded from the study. Unlike the HCs who performed more quickly on eight serial trials of the computerized SDMT, POMS participants initially increased speed though this increase was not sustained across the trials. Reported level of tiredness when completing the test (i.e., “Not at all”, “A little bit”, “Very tired”) was collected. Reported level of tiredness did not differ between MS patients and HCs.

Carroll and colleagues (2019) sought to compare fatigue, psychosocial factors, and neurocognitive functioning across four groups including two POMS groups (15 fatigued patients, 15 non-fatigued patients), a group of 30 participants with chronic fatigue syndrome (CFS), and 30 HCs. Parents of participants also took part in the study. Youth participants in all groups were 15 years of age on average. Half of the POMS participants had severe fatigue assessed with the PedsQL-MFS (Varni et al., 2002), though there were no differences between fatigued and non-fatigued MS participants on any neurocognitive measure using an alpha of .01.

In 2020, Portaccio and colleagues studied 111 POMS and 115 AOMS patients. They found that overall, 34.5% of patients were classified as CI (i.e., failed at least three tests, with failure of a test defined when the score was below the fifth or above the 95th percentile using normative Italian values (Amato et al., 2006)) on the Brief Repeatable Battery of Neuropsychological Tests and the Stroop test. There with no differences in rates of impairment between the pediatric and adult groups. Fatigue measured with the FSS (Krupp et al., 1989) was included in multivariate regression analyses considering prognostic factors for CI, social and professional attainment, unemployment rate, and work complexity. Onset classification (pediatric or adult) was also included along with other variables of interest. Overall, fatigue was not associated with CI, though severity and prevalence of fatigue was not reported and our email request for data/model parameters was unanswered. Older age, higher EDSS, and lower IQ did show an association with CI.

A study by our group (Barlow-Krelina et al., 2021) assessed 65 POMS patients ages eight to 27, and 76 age- and sex-matched HCs between age eight and 29. CI (i.e., impaired performance on four or more of the 15 outcomes) was found in 29.2% of patients compared to 7.9% of controls on the one-hour Penn Computerized Neurocognitive Battery (PCNB; Gur et al., 2012). No significant associations were found between subjective fatigue using the PedsQL-MFS (Varni et al., 2002) and cognition for PCNB (Gur et al., 2012) subtests that differed significantly between groups.

Table 3. Overview of association-related data from included studies

(a) Studies Identifying a Relationship(s) Between Fatigue and Cognition		
Author, Year	**Sample (n), M_{age} (SD; range)**	**Fatigue-Cognitive Association**
Goretti et al., 2012 **same cohort as studies by Amato and colleagues (below)*	**POMS** (n=57), 16.6 (2.5; 11-20)	• PedsQL-MFS self-report total fatigue - Tower of London Test • PedsQL-MFS parent-report total fatigue - Selective Reminding Test – Long Term Storage • PedsQL-MFS parent-report total fatigue - TMT B • PedsQL-MFS parent-report total fatigue - Token Test
Holland et al., 2014	**POMS** (n=26), 15.2 (2.4; 7-18)	• PedsQL-MFS self- and parent-report general fatigue - TMT Part A • PedsQL-MFS parent-report general fatigue - TMT B
Canas, 2014	**POMS** (n=20), 14.8 (2.1, 9-18)	• PedsQL-MFS self-report total fatigue -TMT A
Nunan-Saah, 2015; Nunan-Saah et al., 2017	**2015: POMS** (n=79), 14.5 (2.9; 6.5-18) **2017: POMS** (n=65), 14.6 (3; 6.5-18)	• PedsQL-MFS self- and parent-report total fatigue - BRIEF Global Executive Composite self-report • PedsQL-MFS self- and parent-report total fatigue - BRIEF Global Executive Composite parent-report
Fields, 2021 **statistically significant findings identified in supplemental analyses only*	**POMS** (n=49), 14.1 (2.8)	• PedsQL-MFS parent-report general fatigue and sleep-rest fatigue - Conners CPT HIT RT • PedsQL-MFS parent-report general fatigue - BASC Depression • PedsQL-MFS parent-report cognitive fatigue - DKEFS Trails Visual Scanning • PedsQL-MFS parent-report cognitive fatigue - DKEFS Verbal Fluency (FAS) Switching Total • PedsQL-MFS parent-report cognitive fatigue -DKEFS Sorting Total

		• PedsQL-MFS parent- and self-report cognitive fatigue - DKEFS Verbal Fluency Switching and Sorting • PedsQL-MFS paret-report cognitive fatigue - Conners CPT response time
(b) Studies Not Identifying Relationships Between Fatigue and Cognition		
Title (Author, Year)	**Sample (n), M_{age} (SD; range)**	**Fatigue and Cognitive Assessment**
MacAllister et al., 2005	**POMS** (n=37), 14.9 (2.2; 8-17)	Fatigue: Dichotomous yes/no self-report Cognitive: TMT A, TMT B, Controlled Oral Word Association Test, Boston Naming Test, Listening to Paragraphs subtest of the Clinical Evaluation of Language Fundamentals–III, Wide Range Assessment of Memory and Learning (Verbal Learning and Visual Learning subtests), Beery Test of Visual Motor Integration - 9-hole Peg Test from the MS Functional Composite (to adjust for fine motor functioning)
Amato et al., 2008; Amato et al., 2010; Amato et al., 2014 *same cohort	**2008: POMS** (n=63), 15.3 (2.5; 8.8-17.9) **2010: POMS** (n=56), POMS group 1: 12.5 (1.3; 10.9-14.4), POMS group 2: 17.9 (1.8; 15-20.6) **2014: POMS** (n=48), POMS group 1: 14.5 (0.9; 10-16), POMS group 2: 20.5 (1.9; >16)	Fatigue: Fatigue Severity Scale Cognitive: TMT A, TMT B, Selective Reminding Test and delayed from Rao's battery, Spatial Recall Test and delayed from Rao's battery, SDMT from Rao's battery, Tower of London Test, semantic and phonemic verbal fluency test, oral denomination test from the Aachener Aphasie Test
Charvet et al., 2016	**POMS** (n=108); **CIS** (n=32) *Full sample:* 14.9 (2.6; 5.9-18) **note that only 66 completed self-report measures of fatigue severity*	Fatigue: Fatigue Severity Scale Cognitive: U.S. Network of Pediatric MS Centers Consensus Battery. BASC-2
Bigi et al., 2017	**POMS** (n=27), Median (IQR) 15.7	Fatigue: Reported level of tiredness when completing the test (i.e., "Not at all", "A little bit", "Very tired.") Cognitive: Computer-Based SDMT

Carroll et al., 2019	**POMS** (n=30; 15 fatigued and 15 non-fatigued), 15.9 (9.3-19)	Fatigue: PedsQL-MFS Cognitive: Short-form version of the Wechsler Intelligence Scale for Children - Fourth Edition and in adolescents aged 17 or older using the Wechsler Adult Intelligence Scale - Fourth Edition
Portaccio et al., 2020	**POMS** (n=111)	Fatigue: Fatigue Severity Scale Cognitive: Brief Repeatable Battery of Neuropsychological Tests, Stroop test
Barlow-Krelina et al., 2021	**POMS** (n=65), 18.3 (4; 8-27)	Fatigue: PedsQL-MFS Cognitive: SDMT, Penn Computerized Neurocognitive Battery

Abbreviations. BASC: Behavior Assessment System for Children; BRIEF: Behavior Rating Inventory of Executive Function; CPT: Continuous Performance Test; DKEFS: Delis-Kaplan Executive Function System; PedsQL-MFS: Pediatric Quality of Life Inventory Multidimensional Fatigue Scale; POMS: pediatric-onset multiple sclerosis; SDMT: Symbol Digit Modalities Test; TMT: Trail Making Test

Discussion

We reviewed empirical studies that were published in English between 2001 (following the publication of the first iteration of the McDonald criteria) and July 2022 that included a sample with confirmed diagnoses of POMS using McDonald criteria, and measured fatigue, cognition, and clinical factors including mental health outcomes. We monitored the literature by re-running the searches in the five databases in August 2024. Our search yielded 1275 articles (i.e., 252 more than our initial search). An informal review of these additional titles suggested that none would meet criteria for inclusion in our systematic review.

Clinical and cognitive variables were extracted from 13 publications and two dissertations (encompassing 11 patient groups total due to overlapping patient cohorts). We considered whether it would be feasible to run a meta-analysis based on the quality and amount of evidence available. Due to limitations including the robustness of the findings with the inclusion of few studies, a narrative synthesis was carried out along with a supplemental meta-analysis. Attempts to quantitatively synthesize the POMS fatigue literature continue to be hampered by heterogeneity in the methodology used across studies (i.e., use of different fatigue measures and cognitive test batteries/outcomes, differences in how cognitive impairment is defined, etc.) and approach to statistical analyses including the way in which associations are probed (e.g., correlations or regressions).

It is possible that fatigue may differentially impact adults with MS, as studies in AOMS have failed to find a relationship between subjective fatigue and cognition. Conversely, our narrative synthesis suggests that total fatigue, regardless of whether it is parent- or self-reported, is not reliably associated with overall cognitive functioning, though there may be statistically significant albeit weak associations between fatigue and specific domains of cognitive functioning, particularly performance-based and subjectively reported executive functioning and sustained attention. Results of our supplemental meta-analyses are generally consistent with the above, albeit conclusions were limited by the paucity of independent studies that could be used in this analysis.

Fatigue and quality of life in POMS appeared to be more consistently associated with mood (Carroll et al., 2016; Carroll et al., 2019; Nunan-Saah et al., 2015) as seen in AOMS. It can be challenging to understand the relationship between depression and fatigue due to shared symptoms (Nunan-Saah, 2015). There is also an emerging literature that self-reported measures may be assessing an overall response bias and may not adequately capture the intended outcome (Buchanan, 2016; Shwartz et al., 2020). As such, the studies by Nunan-Saah (2015, 2017) which only show associations between self-reported measures for both fatigue and cognition, may have a lower strength of evidence. Moreover, both fatigue and low mood are common sequelae in MS and may have shared mechanisms including frontal lobe lesions and their connections, neuroinflammatory processes, sleep disturbance, and alterations in neurotransmitter levels that regulate mood and arousal such as serotonin (Ayache & Chalah, 2020; Krupp, 2003). While the neural substrates of fatigue remain inconclusive, researchers examining AOMS have proposed a "multiple disconnection syndrome" caused by brain lesions that alter numerous cortico-cortical and cortico-subcortical connections. Damage to key hubs in the brain may result in patients experiencing a cluster of symptoms including lowered mood, increased or new onset anxiety, and fatigue (Ayache & Chalah, 2020; Calabrese & Penner, 2007). Furthermore, while fatigue is often noted as a symptom of low mood, it is likely that a bidirectional relationship exists between fatigue and mood (e.g., fears about experiencing fatigue or anxiety about the unpredictability of relapses and illness progression may lead to social withdrawal and avoidance of physical activity, subsequently leading to a feeling of isolation, unhappiness, and worry) (Ayache & Chalah, 2020).

It is notable that despite doubling the number of studies compared to the prior review in this area (Carroll et al., 2016), our conclusions are similar. Contemporary studies continue to acknowledge the impact of fatigue in this patient population. However, despite improvements in diagnosis and treatment, the prevalence of severe fatigue in recently published POMS studies does not seem lower than those published in the early 2000s. Specifically, fatigue continues to be prevalent in approximately 20-75% of patients depending on the sample and how fatigue is operationalized and measured. Without a 'gold standard' for the assessment of fatigue, it is hard to know the true prevalence and how rates may differ over time. Moreover, the availability of newer treatments for MS may not necessarily translate to an improvement in fatigue symptoms given that patients may decline treatment (e.g., 41% declined in the 2017 study by Bigi and colleagues).

Limitations and Future Directions

Overall, studies were limited by small sample size (often a constraint in the POMS literature due to the rarity of the disease), variable clinical and demographic characteristics, diverse methodology (i.e., researchers adopting different test batteries and definitions of cognitive impairment), and lack of adjustment for multiple comparisons potentially inflating the possibility of a Type 1 error, thus lowering the quality of those studies.

It is also notable that not all studies included in this review were designed to answer the question of whether there is a relationship between fatigue and cognition. Moreover, it is difficult to assess whether fatigue differentially affects certain cognitive domains more than others. For example, in Barlow-Krelina et al., (2021), we examined associations between task performance and clinical predictor variables (including age at disease onset, disease duration, neurological disability, fatigue, and emotional distress) only for cognitive outcomes that differed between POMS and HCs. Since group differences in cognitive performance were mainly observed on measures of executive functioning, immediate recognition memory, and complex cognition (i.e., verbal and non-verbal reasoning), relationships between fatigue and other domains, such as social cognition, were not examined. It is also possible that patients with the greatest degree of fatigue did not enroll in our study, which may limit the generalizability of our findings to the POMS population. It is also possible that crude ratings of tiredness, without utilizing a validated fatigue measure (i.e., Bigi et al., 2017; MacAllister et al., 2005), may not adequately capture cognitive fatigue (described further in the 2017 study by Bigi and colleagues). Like the pain literature, it can be hard to quantify seemingly subjective phenomenon (Robinson-Papp et al., 2015). Additionally, many fatigue measures are often retrospective whereby respondents reflect on their fatigue in the past month for example. There is likely a role for functional imaging studies to capture patterns of brain activation, or effort, as participants perform a cognitively demanding task(s) (DeLuca et al., 2009). This can be complimented with in-vivo measures of cognitive or state levels of fatigue pre- and post-task.

Conclusions

Fatigue and cognition are not consistently associated in POMS. Some domains of cognition, namely executive functioning and sustained attention, appear to be more sensitive to fatigue than others. The finding of a relationship between subjectively reported executive function challenges and subjective fatigue in Nunan-Saah et al., (2017) may suggest that the findings between fatigue and performance-based measures such as the TMT may reflect both motor demands and aspects of executive functioning, not just the former. In this case, specifically working memory and switching. Further evidence for this comes from studies like the dissertation by Fields (2021). Considering the significant impact of fatigue on the quality of life in patients with POMS, more studies are needed to better understand determinants of fatigue, how to measure fatigue, and the role fatigue plays on cognition.

Chapter 3: Fatigability on a Sustained Attention Task and Whole Brain White Matter Microstructure in Pediatric-Onset Multiple Sclerosis (POMS)

Abstract

Background and Objectives

A unified taxonomy to inform the assessment and management of fatigue in neurologic populations was introduced by Linnhoff and colleagues in 2019. It differentiates subjective fatigue from fatigability. Fatigability, operationalized as an objectively quantifiable change in performance over time, can be examined using measures of within-subject variability, known as intra-individual variability (IIV). Cognitive fatigability has been defined as challenges with maintaining consistent performance throughout a sustained cognitive task.

Whether IIV is a behavioural marker of fatigue remains unknown, and to our knowledge has not been studied in pediatric-onset multiple sclerosis (POMS). In adults with multiple sclerosis (MS) and other neurological populations, slower and more variable information processing has been related to white matter differences.

We sought to: 1) characterize the prevalence of parent- and self-reported fatigue in POMS relative to healthy controls (HCs), 2) assess whether individuals with POMS show differences on the primary novel outcome of IIV (i.e., fatigability), and the secondary outcomes of accuracy and mean response time on an abbreviated version of the Continuous Performance Test (CPT) relative to HCs, 3) examine respective associations between subjective fatigue and the primary and secondary outcomes on the CPT, and 4) determine whether whole brain white matter integrity associates with the primary and secondary outcomes on the CPT. Results with accuracy and mean response time were presented to contextualize the IIV findings and

specifically examine whether IIV may be more sensitive to between-group differences than traditional measures of sustained attention.

Materials and Methods

We compared 35 POMS participants (M_{age}=17.4±3.0 years; 24 female, average disease duration=3.01±3.33 years) and 70 age- and sex-matched HCs (M_{age}=18.4±4.9 years; 48 female) recruited from the Canadian Pediatric Demyelinating Disease Study (CPDDS). A subsample (i.e., 30 POMS, 51 HCs) had diffusion tensor imaging (DTI) data available. The Pediatric Quality of Life Inventory™ Multidimensional Fatigue Scale (PedsQL-MFS) was completed by each participant and one of their parents. IIV (i.e. fatigability) was assessed using two metrics, the individual standard deviation (ISD) and the coefficient of variation (COV), based on performance on an abbreviated version of the CPT from the Penn Computerized Neurocognitive Battery (PCNB). Whole brain fractional anisotropy (FA) was used as the primary DTI metric and a proxy of whole brain white matter microstructure.

Results

Severe total fatigue was more commonly endorsed in the POMS group by both parents (42.9%) and patients (36.4%) relative to the HC group (14.3% and 12.1%, respectively, p=.01). While POMS and HCs did not differ significantly in mean response time on the CPT (p=.42), POMS demonstrated greater IIV measured as both ISD (p=.01) and COV (p=.001) and were less accurate (p=.02) relative to HCs. Overall, parent- and self-rated symptoms of fatigue did not significantly associate with the CPT metrics of fatigability (i.e., IIV) when collapsed across groups or within each group. However, contrary to our expectations, slower response time was associated with fewer symptoms of sleep-rest fatigue as reported by POMS participants (p<.01). Mean ± SD whole brain FA was significantly lower (p<.001) in POMS (0.188±0.00) relative to

HCs (0.194±0.00) and while generally in the expected direction, mean whole brain FA was not significantly associated with IIV, accuracy, or mean response time on the CPT in POMS (all *p* values >.01). Reduced sample sizes for brain-behaviour analyses may have underpowered the regression analyses.

Conclusions

Severe fatigue reported by patients and their parents is three times higher than that reported by healthy peers and their parents. While POMS patients are more susceptible to greater fatigability (i.e., greater response time variability) and reductions in accuracy relative to healthy peers, these behaviours were not consistent with subjective report of fatigue. This may suggest that subjective and performance-based measures of fatigue may be assessing different constructs, though other interpretations are discussed. Finally, the pattern of findings regarding the brain-behaviour analyses suggests that IIV associates with global white matter integrity in POMS, albeit non-significantly.

Introduction

Severe fatigue as reported on symptom-specific measures is prevalent in approximately 40% of POMS patients and can adversely impact quality of life (Carroll et al., 2016). Many different self-report rating scales are used to assess fatigue, though some are not specific to MS or have not been validated for younger MS patients (Amato et al., 2014). Fatigue has been defined as feelings of "tiredness" or "sleepiness," "loss of energy," or reduced "drive" (Wylie & Flashman, 2017). Some questionnaires such as the PedsQL-MFS (Varni et al., 2002) assess different dimensions of fatigue, like cognitive, physical, and emotional, and produce scores on these different subscales along with an overall fatigue score, whereas others like the Fatigue Severity Scale (Krupp et al., 1989) for example, are unidimensional (Linnhoff et al., 2019).

Fatigue is a difficult phenomenon to study. Fatigue often overlaps with other conditions such as anxiety, depression, and sleepiness/sleep disorders. These complicate the study of fatigue as a distinct phenomenon. Moreover, the notion of fatigue is somewhat elusive making it difficult to isolate specific causes and study them independently (Carroll et al., 2016; Walker, Lindsay-Brown, & Berard, 2019). When studying or working with the pediatric and adolescent population, it is also vital to consider that differences may exist between a parent and their child's perception of fatigue. For these reasons, few studies have sought to explore mechanisms or correlates of fatigue (Veauthier & Paul, 2014).

Kluger, Krupp, & Enoka (2013), introduced a unified fatigue taxonomy that differentiates *perceived fatigue* from *performance fatigability*; the latter classified as either cognitive or physical. They also outlined major factors thought to contribute to perceived fatigue (homeostatic and psychological factors), and performance fatigability (peripheral and central nervous system factors).

More recently, Linnhoff and colleagues (2019) proposed an updated, more comprehensive framework for informing the assessment of fatigue in MS. Specifically, their classification speaks to physical and cognitive fatigue (which can be subdivided into subjective fatigue and objective fatigability), and psychosocial fatigue (solely subjective fatigue).

Fatigability can be operationalized as an objectively quantifiable change in how a task is performed (Morrow, Rosehart, & Johnson, 2015; Walker, Lindsay-Brown, & Berard, 2019). While there is no gold standard approach for the behavioural measurement of cognitive fatigability (Barrios et al., 2022; Bruce, Bruce, & Arnett, 2010; Linnhoff et al., 2019), as noted in the Linnhoff et al., (2019) model, cognitive fatigability can be operationalized as fluctuations in response time or accuracy performance on tasks requiring sustained mental effort. For example, one might look at IIV in response time on a sustained attention task such as the CPT. Another approach is to compare performance on the same task administered before and after a perceived "fatiguing" test is completed (Barrios et al., 2022). Studies have shown that changes in IIV over time align better with individuals' perceptions of fatigue relative to mean level performance.

Moreover, IIV in performance is increasingly considered a metric of cognitive fatigability (Wang, Ding, & Kluger, 2014). IIV has been found to be sensitive to cognitive changes in neurologic and clinical populations and is a well documented behavioral feature in individuals with brain lesions (Aldughmi, Bruce, & Siengsukon, 2017; Bruce, Bruce, & Arnett, 2010; Chiang et al., 2022; Haynes et al., 2015; Roalf et al., 2014; Mazerolle et al., 2013; Wang, Ding, & Kluger, 2014; Wiker et al., 2023; Wojtowicz, Berrigan, & Fisk, 2012; Wylie & Flashman, 2017) and chronic fatigue syndrome (Fuentes et al., 2001).

The connection between IIV and fatigue is supported by shared neural mechanisms. Both IIV and fatigue involve neural changes, particularly in the prefrontal cortex utilizing functional imaging and selective attention tasks (Kelly et al., 2008), and alterations in neurotransmitter systems, such as dopamine and norepinephrine (Wang, Ding, & Kluger, 2014). These are thought to contribute to reduced cognitive control and greater inconsistencies in performance during an acute task requiring sustained mental effort (Wang, Ding, & Kluger, 2014). It may also be that tasks mediated by the prefrontal cortex are more sensitive to the effects of cognitive fatigue, as such, these tasks are most impacted by fatigue because of the effort required for inhibition and sustained focus.

Slower and more variable information processing has also been related to white matter differences in adults with MS (Mazerolle et al., 2013). Mazerolle et al (2013) found that IIV was more sensitive than response time to overall white matter burden, though the precise structural and functional mechanisms (e.g., impaired neuronal transmission and connectivity, inflammation resulting in neurochemical changes/neurotransmitter disruption) underlying this relationship remain unclear.

IIV is a manifestation of mental fatigue and reduced arousal, particularly on effortful tasks such as those requiring sustained attention and inhibitory control. IIV can be used as a behavioural marker to measure the impact of mental fatigue and reduced arousal. Neurologically, IIV may capture neural noise which may worsen over the course of performing an effortful task (Mazerolle et al., 2013), and reduced white matter integrity (Akbar et al., 2016); both are well documented in POMS. In sum and considering previous findings in POMS regarding reduced attention and processing speed, investigating IIV in POMS is essential to understand cognition in a more nuanced way in the pediatric population (Till et al., 2011).

Therefore, the current study aimed to examine IIV as a measure of fatigability in individuals with POMS and its potential association with subjective fatigue and whole brain white matter microstructure. In summary and more directly, we set forth the following objectives:

Aim 1: To assess whether individuals with POMS show differences on the primary novel outcome of response time IIV (i.e., fatigability) and the secondary outcomes of accuracy and mean response time on the CPT relative to matched healthy controls.

Hypothesis 1: Patients will demonstrate greater fatigability evidenced by higher IIV (i.e., higher ISD and COV), reduced accuracy, and slower mean response time on the CPT relative to matched healthy controls.

Aim 2: To examine the respective associations between subjective ratings of fatigue (parent and self) on the PedsQL-MFS and the primary (i.e., IIV) and secondary (i.e., accuracy and mean response time) cognitive outcomes from the CPT in POMS.

Hypothesis 2: Lower scores on the parent- and self-report PedsQL-MFS, indicative of greater fatigue, will be associated with greater IIV on the CPT. The associations between subjective measures of fatigue and IIV will be stronger relative to associations with accuracy and mean response time.

Aim 3: To examine whether IIV as well as the secondary cognitive outcomes on the CPT are associated with whole brain white matter integrity using FA in POMS.

Hypothesis 3: Greater IIV, reduced accuracy, and slower mean response time on the CPT will be associated with reduced whole brain white matter microstructure (i.e., lower FA) for patients.

Materials and Methods

Participants

Data for the multi-site, longitudinal CPDDS which included 23 sites across Canada and the Children's Hospital of Philadelphia were collected between 2004 and 2019. The study included an incident cohort of pediatric patients with acquired demyelinating syndromes (ADS) and HCs. Research ethics approval was obtained by all participating institutions. Written informed consent was obtained from participants or a parent/legal guardian.

Neurocognitive data were acquired between 2015 and 2019 for prospectively monitored, English-speaking children and youth with ADS who had evidence of a relapsing course (i.e., clinical attacks or new MRI lesions greater than 30 days from onset); their data contributed to Phase 3 of the national study. Baseline neurocognitive and neuroimaging data were used in this dissertation.

POMS patients were within 90 days of disease onset at time of enrolment and met diagnostic criteria for MS (Thompson et al., 2018). Patients must have experienced their first demyelinating event prior to age 18, although some patients were older than 18 at the time of enrolment given the 90-day interval from attack. Only patients with a confirmed diagnosis of POMS were included in the current analysis; patients identified as having demyelination associated with myelin oligodendrocyte glycoprotein antibody disease (MOGAD), anti-Aquaporin 4 related neuromyelitis optica spectrum disorder (NMOSD), or monophasic disease were excluded from the analytic dataset. Healthy controls (i.e., children and youth without demyelinating disease or disability preventing completion or impairing cognitive test performance) were enrolled between 2015 and 2019 using flyers and web-based advertising.

Participants were excluded from the present analyses if they had prior exposure to the assessment battery or were deemed to have insufficient visual/motor ability to perform cognitive testing. The latter was of particular importance given that the cognitive outcome has a high loading on visual acuity and motor ability.

To mitigate the impact of known challenges with response time measurement in this multi-site study (e.g., variable internet speed at the different sites), our analytic sample was restricted to only include data from The Hospital for Sick Children because this site yielded the largest neurocognitive data pool; 35 of 70 POMS participants and 70 of 109 HCs were assessed at The Hospital for Sick Children and had valid data (Figure 6). A subsample of participants with cognitive data also had DTI data available from research magnetic resonance imaging (MRI) scans (i.e., 30 POMS, 51 HCs).

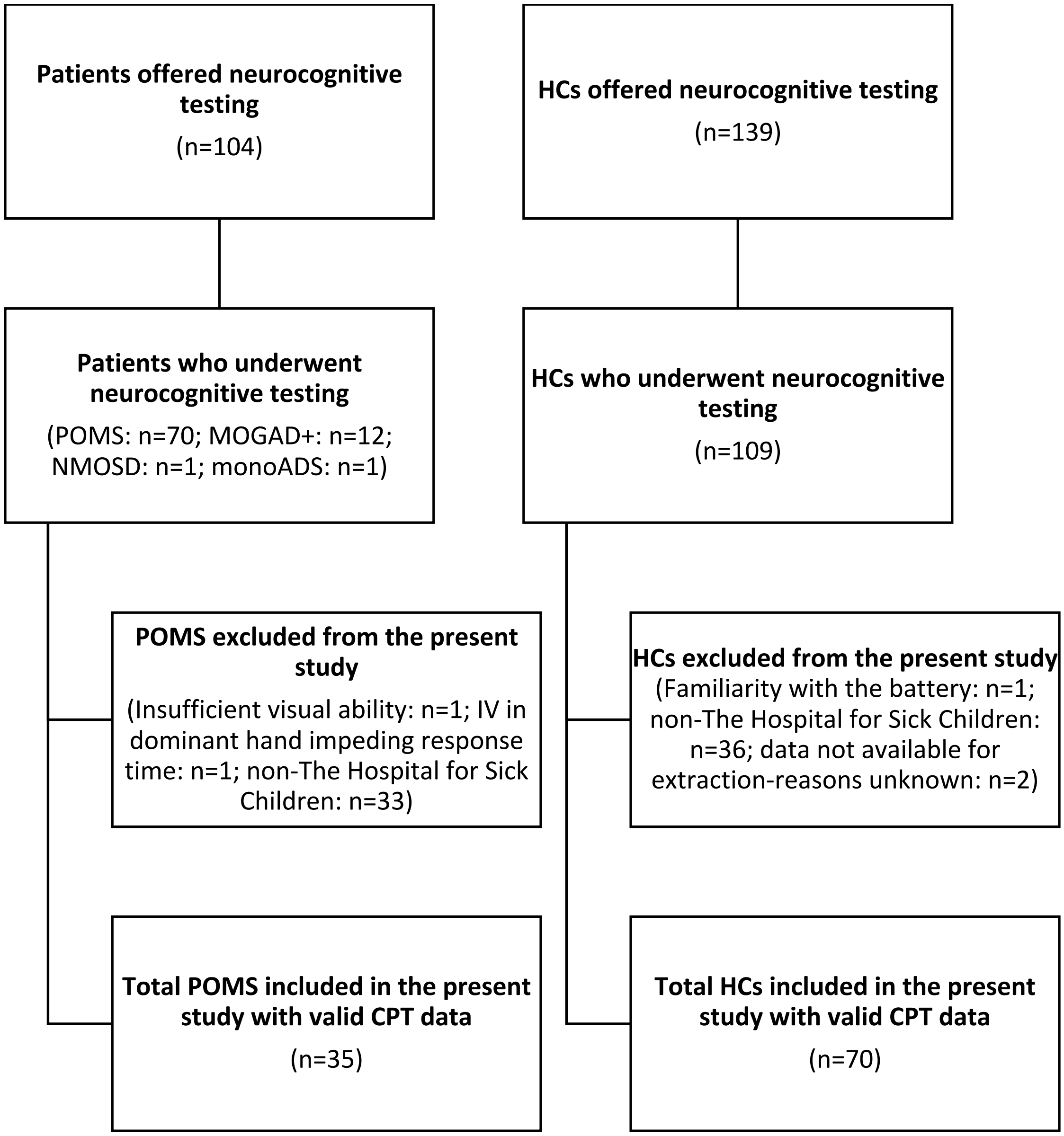

Figure 6. *Study enrolment*

Measures

Fatigue Evaluation. We measured parent- and self-reported fatigue using the respective versions of the PedsQL-MFS (Varni et al., 2002). The questionnaire includes 18 items, six in each of three scales – general fatigue (e.g., feeling too tired to do things that you want to do), sleep-rest fatigue (e.g., sleeping a lot), and cognitive fatigue (e.g., difficulty thinking quickly, holding attention). The questionnaire asks how much of a problem each item has been *in the past month.* Each item is rated on a five-point Likert scale ranging from "almost never" to "almost always". Total scores range from 0 to 100, with higher transformed scores reflecting fewer problems (Varni et al., 2002). Participants with scores less than two standard deviations (SDs) from the published Varni et al., (2010) control means were considered to have severe fatigue (MacAllister et al., 2009; van Deuren et al., 2020). The reliability and validity of the PedsQL-MFS (Varni et al., 2002) (and its language translations) have been demonstrated in pediatric rheumatic disease and other medical populations as well as in university students (e.g., Varni et al., 2002; Varni, Burwinkle, & Szer, 2004; Varni & Limbers, 2008; Varni et al., 2010).

Given that the PedsQL-MFS (Varni et al., 2002) is designed to capture fatigue in the past month, only questionnaire data completed within 30 days from neurocognitive data were included. Self-report data were available for 33 of 35 POMS (94.3%) participants and 58 of 70 HCs (82.9%). Parent-report data were available for 28 of 34 POMS participants (82.4%) and 42 of 70 HCs (60.0%). Across all participants with included data, 83.5% completed the self-report questionnaire on the same day as cognitive testing and 81.4% of parents completed the questionnaire on the same day as cognitive testing. The median number of days between the self-report questionnaire completion and cognitive assessment was zero days (range: 0-30). The median for the parent-report was also zero days (range: 0-29). Data from participants who completed the questionnaire on a day outside of the cognitive assessment did not look significantly different from participants who completed both assessments on the same day (data not shown for brevity).

Cognitive Evaluation. The present study used the Continuous Performance Test - Number/Letter Version, herein referred to as the CPT from the children's version of the PCNB (Gur et al., 2001; Gur et al., 2010; Roalf et al., 2014). The PCNB takes approximately one hour to complete. The battery assess executive function (i.e., abstraction and flexibility, working memory, and attention), episodic memory (i.e., face, object, and word recognition memory), complex cognition (i.e., language, nonverbal, and spatial reasoning), social cognition (i.e., emotion recognition and emotion and age differentiation), and sensorimotor function.
The order of presentation of these tests is consistent between participants to maintain engagement and prevent fatigue (Gur et al., 2012). The CPT is the twelfth of fourteen subtests in the PCNB. The battery was administered by a trained assessor using a standardized administration protocol. Breaks were offered at standardized intervals approximately every 15 minutes. A table presenting the PCNB subtests in order is included as Supplemental Table A.

Each test on the PCNB provides a measure of both accuracy (i.e., number of correct responses) and response time (or efficiency of responding), with the exception of sensorimotor tests specifically designed for measuring motor speed. The PCNB has high sensitivity for detecting cognitive impairment in youth with different neuropsychiatric and medical conditions (Gur et al., 2014; Merikangas et al., 2017; Thomas et al., 2013; Ibrahim et al., 2016) and has been used to probe well-established brain systems with functional neuroimaging (Roalf et al., 2014). Pediatric and adult versions have been developed with acceptable construct validity and psychometric properties (Gur et al., 2001; Roalf et al., 2014; Gur et al., 2010).

The CPT was selected to evaluate fatigability given its monotonous and attention-demanding nature. Moreover, the minimal learning in this task is thought to make it a purer test for fatigue assessment. Individuals experiencing fatigue are more likely to have difficulty sustaining the attention required to maintain strong performance over this three-minute test (e.g., Berard, Smith, & Walker, 2018; Linnhoff et al., 2019) and this may result in greater response time IIV among POMS participants relative to HCs. As well, the CPT which requires prolonged attention measures both visual sustained attention and vigilance. Tasks of this nature have been shown to be susceptible to internal interference which can contribute to greater IIV (Linnhoff et al., 2019). In the study by Aldughmi, Bruce, & Siengsukon (2017), the CPT was used as the measure of cognitive fatigability and was the only task of two other motor fatigability measures to associate with subjective report of fatigue. Finally, the relationship between fatigue and performance on sustained attention tasks is thought to be underlied by shared brain regions including alterations in the fatigue circuit (described later).

The PCNB also includes a Go-No-Go task that also demands sustained attention. However, the CPT was selected over the Go-No-Go given that stimuli presentation is slower paced and has more foils than targets, while Go-No-Go taps more into inhibition since stimuli presentation is faster paced and there are many more targets. In addition, Go-No-Go is more newly implemented and is backed by less literature (Gur et al., 2012).

On the CPT, participants are instructed to press the spacebar whenever they perceive a set of lines that form a complete and correctly oriented number (resembling numbers on a digital clock; Figure 7) or letter. The version of the CPT used includes 180 trials in total. Number trials comprise the first half of the test, followed by a second block of letter trials. One third (n=30) of each number and letter trials are targets and two thirds (n=60) of each are foils.

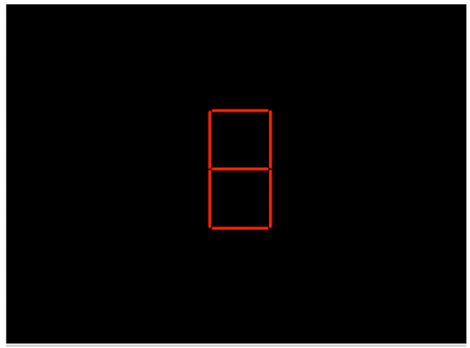

Figure 7. *Test screenshot of a target for PCNB CPT number trials*

Each block lasts a minute and a half. Each stimulus flashes for 300 milliseconds followed by a blank page displayed for 700 milliseconds, giving the participant one second to respond to each trial. The participant practices both types of trials before the task begins.

Two methods were used for the calculation of IIV for all participants: ISD and COV. As discussed in Wojtowicz, Berrigan, & Fisk (2012), ISD and COV provide different estimates of IIV. Given the novelty of looking at IIV in POMS, we examined both ISD and COV; the latter controls for mean response time, reducing the impact of the individuals' mean-level performance on standard deviation. Raw ISD provides information on the consistency (or inconsistency) of an individual's performance over time. COV in this context may be more informative as it elucidates whether the variability is unusually high relative to mean performance – there were both clinical and research implications for including both given the aim of elucidating sensitive behavioural markers of fatigability.

IIV was calculated using data from all trials administered. Variability by blocks (i.e., number trial versus letter trial blocks) was also considered. ISD was calculated as the standard deviation in response time (and for trials within each block); COV, expressed as a percentage, was calculated by dividing the standard deviation of response time by mean response time and multiplying by 100 (Wojtowicz, Berrigan, & Fisk, 2012).

Accuracy, expressed as percentage of correct responses, was manually calculated by summing true positive responses in each half of the test, dividing by 60 (i.e. total number of correct letters and numbers) and multiplying by 100. Other cognitive outcomes included mean response time, perseverations (i.e., the total count of responses provided under 200 milliseconds), and errors of omission and commission (Gur et al., 2001; Kurtz et al., 2001). Detectability (d') was calculated using the *psycho* package in R (Makowski, 2018). Detectability provides an index of how well the participant can discriminate between a target and a foil and corresponds to the z-score of hit rate subtracted from the errors of commission.

In addition to the CPT, we also considered participants' performance on the Finger-Tapping Task from the PCNB. This task was selected to evaluate motor speed as it most closely mirrors the motor demands of the CPT (i.e., quick and frequent pressing of the spacebar using the pointer finger). Finger tapping tests have been used to assess motor performance in children and adults with MS, stroke, and other neurological diseases (e.g., Parkinson's disease). In adults with MS, finger-tapping performance has been associated with disability measured by EDSS. Moreover, the task is considered to be a valid and reliable measure of sensorimotor function in this population (Gulde et al., 2021). Taken together, given the prevalence of motor challenges in this population, it is important to evaluate sensorimotor speed and control for it should group differences be identified. This ensures that differences in response time (if observed) are over-and-above performance on simple motor tasks.

During neurocognitive testing, the assessor noted behavioral and/or environmental observations pertinent to testing (e.g., presence of distractions, motivation towards the task, misunderstanding of instructions, and technical problems). Upon completion of the battery, data were sent to the PCNB team at the University of Pennsylvania where quality control procedures were applied to each participant's dataset. The data were plotted on a scatterplot to examine outliers (accuracy plotted on the Y axis and speed on the X axis). The data were then transferred via a data transfer agreement to The Hospital for Sick Children and later to York University where the data underwent further quality control procedures (i.e., examination of assessor comments and removal of invalid participant data, checking for outliers, and Winsorizing).

Neuroimaging. The median number of days between the MRI and cognitive assessment was zero days (range: 0-330) with 75.3% of scans performed on the same day as cognitive testing; one HC and two MS participants underwent an MRI scan more than three months following cognitive evaluation. Structural MRI scans at The Hospital for Sick Children were performed on either a Siemens Verio or Simens PRISMA Fit 3T scanner according to a standardized research protocol conforming to rigorous operating procedures. Acquisition parameters are described in Supplemental Table B.

Images underwent quality control examinations to assess for motion artifacts or signal dropouts. Lesions were identified on fluid attenuated inversion recovery (FLAIR) images using Lesion Segmentation Toolbox (Schmidt et al., 2019), manually edited (if required), and in-painted on the Magnetization Prepared Rapid Gradient Echo (MPRAGE) images to look like the surrounding normally appearing voxels (Fabri et al., 2021).

DTI data processing was conducted using the FMRIB Software Library (FSL; Jenkinson et al., 2012). Preprocessing of the images involved correction for MRI eddy current distortions using the non-linear tool of the same name. Non-linear registration to a reference volume (b=0) was also used to correct for head motion. Brain masks were generated using the Brain Extraction Tool in FSL and applied to the diffusion images to remove the skull. A diffusion tensor model was fit at each voxel of the skull-stripped diffusion images using the DTIFIT tool in FSL. Finally, T1 images were registered to the diffusion images to ensure alignment of the anatomical structures in both sets of images. DTI analyses were computed with lesions, to include the impact of pathology on whole brain white matter microstructure. Each DTI metric was harmonized by ComBat (a computer algorithm that estimates scanner-related variability in the data) separately.

Mean whole brain white matter FA, indicative of the directionality of water diffusion, was used as the primary DTI metric in this study. Of the measures derived from fitting the data to a diffusion tensor model (i.e., FA, mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD)), FA is thought to be a more sensitive metric for detecting change in white matter microstructure (Haddad et al., 2022).

Clinical Evaluation. A standardized study case report form was used to document demographic and relevant medical histories. Date of disease onset and type of treatment with disease-modifying therapies (DMTs) were documented, and an Expanded Disability Status Scale score (EDSS; Kurtzke, 1983) was approximated by study site neurologists. Though the numbers of prior attacks was reported, the study was not formally designed to measure relapse rate.

Socioeconomic status was measured using the Barratt Simplified Measure of Social Status (Barratt, 2006), yielding a total education and occupation score for both parents. Participants also reported the number of years of education completed by themselves and each of their parents; parental education values were averaged. If only one value was reported for parental education, that parent's score was used for the parental education variable.

Symptoms of depression and anxiety were measured using the Paediatric Index of Emotional Distress (PI-ED; O'Connor et al., 2016) and the Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983) for participants under and over age 16, respectively. Both are 14-item questionnaires that generate an emotional distress score, based on a combined depression and anxiety score. Scores on both the PI-ED and HADS range from 0 to 42, with a score greater than 20 indicating clinically significant emotional distress (O'Connor et al., 2016).

As described previously, fatigue and depression are both common in MS with shared features. These presentations may also have shared mechanisms including damage to brain hubs (Ayache & Chalah, 2020; Calabrese & Penner, 2007; Krupp, 2003; Nunan-Saah, 2015). Previous studies have also identified that depression associates with self-reported fatigue and the taxonomy by Kluger, Krupp, and Enoka (2013) advocates that clinical studies should include measures of perceived fatigue, fatigability, and physiological/psychological factors.

Statistical Analyses

Descriptive statistics were examined for the clinical characteristics of the MS sample, including EDSS, age at disease onset, DMT use, disease duration, number of prior attacks, and T1 and T2 lesion volumes. Differences between POMS and HCs on demographic variables (i.e., age, sex, level of education, years of parental education, and socioeconomic status), emotional distress, and fatigue were examined with Welch's t-tests and chi-square tests, where appropriate. Intra-class correlation coefficients (ICC) were calculated to analyze the association between parent and child fatigue scores. The proportion of POMS and HCs classified as severely fatigued on the PedsQL-MFS (Varni et al., 2002) parent- and self-reports was compared with Fisher's Exact Test.

Aim 1: Few extreme cases (i.e., ± 3SD from the mean of each group) were identified. This included one HC (not consistently the same participant) on outcomes including ISD, COV, accuracy, omissions, commissions, and perseverations. Additionally, one POMS participant was identified (not consistently the same individual) as an outlier on accuracy (i.e., reduced performance), omissions, and commissions. These participants were retained in analyses and their data Winsorized.

Multiple linear regression controlling for age, sex, and parental education were used to identify whether POMS differed from HCs on CPT outcomes. First, performance on the PCNB tapping task was evaluated to ensure that groups did not differ in their motor speed which could confound subsequent response time analyses. Next, groups were compared on IIV (i.e. ISD and COV), and the secondary core outcomes on the CPT, including measures of accuracy, errors, and mean response time, all controlling for relevant covariates. IIV analyses included all trials where a response was given (i.e., correct trials and errors of commission). Observing the overall fluctuations in performance, not just response time on correct trials allowed for the observation of overall patterns of performance.

Aim 2: Spearman bivariate correlations (two-tailed) were used to examine the association between IIV on the CPT and subjective ratings of fatigue (parent and self) on the PedsQL-MFS for POMS patients, HCs, and collapsing across groups. Associations between accuracy and mean response time with subjective fatigue were also explored as a comparison to the observed associations with IIV.

Aim 3: Multiple linear regressions with age and sex included as covariates assessed group differences in whole brain DTI metrics. Associations between ISD and COV respectively, and FA on the CPT were then examined with multiple linear regression (controlling for age, sex, and parental education) each in the POMS and HC groups. Unstandardized beta coefficients were adjusted by dividing by 100 to yield more interpretable findings; effect estimates were reported to indicate the change in the cognitive outcome per 0.01 increase in FA.

Analytic Notes. An alpha of .05 was used to assess statistical significance for all demographic and between-group cognitive and DTI analyses. The *p*-value was adjusted to .01 for correlation and brain-behaviour analyses in the second and third aims to reduce the likelihood of a Type 1 error due to the multiple comparisons conducted. Effect sizes were also considered in the interpretation of correlation coefficients according to the guidelines by Cohen (1998) whereby .10-.29 is small, .30-.49 is moderate, and .50-1.0 is large (Gignac & Szodorai, 2016).

Assumptions underlying linear regression were tested statistically and visualized using plots (i.e., residuals versus fitted values, normal Q-Q plot, residuals versus predictor, Cook's distance, and leverage) for all regression models. Where there were concerns regarding slight deviations in assumptions (i.e., homogeneity of variance and normality), robust estimation, specifically sandwich estimation was used to ensure a more reliable standard error and *p* value.

Sensitivity Analyses. Two sensitivity analyses were also performed. The first involved re-running the main analyses (i.e., Aims 1-3 described above) using data from correct trials only. The second involved imputing the maximum time (i.e., 1000 milliseconds) for omissions and re-running the analyses including data from all trials (i.e. correct, commission, and omission responses). We also looked qualitatively to assess whether responses following an omission error were given in under 200 milliseconds (i.e., a "perseverative error" as labeled by the task).

Results

Sample Characteristics

Demographic and disease-related characteristics of the sample are reported in Table 4. Groups did not differ significantly with respect to age, sex, or emotional distress (all *p* values >.05), though mean level of education was slightly higher in the HC group (*p*=.05). Groups differed significantly with respect to parental education and socioeconomic status (*p*=.02) with lower mean levels in the POMS group. Parent-reported levels of total and general fatigue, but not cognitive fatigue, were significantly lower in the POMS group relative to HCs (*p*<.05). Groups did not statistically differ on self-reported measures of fatigue. Given that groups were comparable on reported emotional distress, the observed differences in fatigue are unlikely to reflect mood-related differences.

The ICCs indicated moderate agreement between parent- and self-ratings of total fatigue (ICC=0.59), general fatigue (ICC=0.61), sleep-rest fatigue (ICC=0.47), and cognitive fatigue (ICC=0.58) (all *p* values ≤.001) collapsing across groups. ICCs were slightly higher when comparing parent and self-ratings in the POMS group: total fatigue (ICC=0.72), general fatigue (ICC=0.67), sleep-rest fatigue (ICC=0.71), and cognitive fatigue (ICC=0.58) (all *p* values ≤.001). As expected, parent- and self-reported total fatigue were associated with emotional distress using the HADS/PI-ED with r values of .38 and .34, respectively (both *p* values=.002).

POMS participants were tested at variable intervals from disease onset, ranging from approximately four months to 11 years; 28 of 35 (80%) patients were described as having a disease duration of less than five years with an average of 3.0 years (SD=3.3). Age at MS onset ranged from 8.6 to 17.9 years (M=14.9, SD=2.0), with only four of 35 (11.4%) having their first attack prior to age 12 years. MS patients had a median EDSS score of 1.5 ranging from one through 3.5, and 26 of 35 (74.3%) patients were receiving disease modifying treatment at the time of the assessment.

Table 4. Demographic and clinical characteristics

Characteristic	n	POMS (n=35) M±SD / N (%)	n	HC (n=70) M±SD / N (%)	p/X^2	Cohen's d/ Cramer's V
Age at testing (years)	35	17.4 ± 3.0 (13-24)	70	18.4 ± 4.9 (8-29)	.21	.22
Sex (male/female, % female)*	35	11/24 (68.6%)	70	22/48 (68.6%)	1.0	.00
Participant education (years)	35	11.1 ± 2.3 (7-18)	70	12.4 ± 3.9 (2-20)	.05	.36
Parental education (years)†	34	14.3 ± 2.0 (11-19)	63	15.3 ± 2.1 (10-20)	**.02**	.51
Socioeconomic status†	20	38.3 ± 16.8 (13-61)	37	48.1 ± 10.0 (29-66)	**.02**	.77
Emotional distress† (normal/high, %)*	34	32/2 (5.9%)	56	53/3 (5.4%)	1.0	.00
Participant fatigue						
Parent-rated total fatigue†	28	72.2 ± 23.6 (1-100)	42	83.1 ± 15.2 (46-100)	**.04**	.57
General fatigue	28	70.2 ± 25.4 (4-100)	42	83.2 ± 15.8 (46-100)	**.02**	.64
Sleep-Rest fatigue	28	71.2 ± 25.7 (0-100)	42	81.3 ± 17.5 (25-100)	.08	.48
Cognitive fatigue	28	75.3 ± 26.9 (0-100)	42	84.7 ± 17.6 (29-100)	.11	.43
Self-rated total fatigue†	33	69.2 ± 21.1 (26-99)	58	72.0 ± 15.3 (14-96)	.51	.16
General fatigue	33	71.7 ± 21.9 (25-100)	58	76.0 ± 17.2 (4-100)	.34	.23
Sleep-Rest fatigue	33	64.6 ± 21.3 (33-100)	58	65.9 ± 15.0 (25-92)	.76	.07
Cognitive fatigue	33	71.2 ± 26.3 (0-100)	58	74.0 ± 20.7 (0-100)	.61	.12
EDSS (median, range)	35	1.5 (0-3.5)	-	-	-	-
Age at disease onset (years)	35	14.9 ± 2.0 (9-18)	-	-	-	-
DMT at testing (N/Y, %)	35	9/26 (74.3%)	-	-	-	-

Disease duration (months)	35	36.2 ± 39.9 (3.9-133.9)	-	-	-	-
Number of prior attacks (median; range)	35	1.0 (1-7)	-	-	-	-
T2 lesion volume (cm^3; median, range)	31	3.42 (0.03-42.76)	-	-	-	-
T1 lesion volume (cm^3; median, range)	26	0.40 (0-8.96)	-	-	-	-

Abbreviations: DMT: Disease Modifying Therapy; EDSS: Expanded Disability Status Scale; HC: healthy control; POMS: pediatric-onset multiple sclerosis
Note.†data missing (per n column); *chi-square

Fatigue

To elaborate on the mean-level fatigue data presented in Table 4, the prevalence of severe fatigue in POMS and HCs was characterized; data are presented in Table 5. Severe total fatigue was more commonly endorsed in the POMS group by both parents (42.9%) and patients (36.4%) relative to the HC group (14.3% and 12.1%, respectively, *p*=.01).

Table 5. Proportion of POMS and HC participants classified as reporting severe fatigue on the PedsQL-MFS parent- and self-report

		POMS		**HC**	
PedsQL-MFS	n	N Severe (%)	n	N Severe (%)	*p*
Parent-rated Total†	28	**12**(42.9%)	42	**6**(14.3%)	**.01**
General Fatigue	28	**11**(39.3%)	42	**7**(16.7%)	.05
Sleep-Rest Fatigue	28	**8**(28.6%)	42	**6**(14.3%)	.22
Cognitive Fatigue	28	**7**(25%)	42	**2**(4.8%)	**.02**
Self-rated Total†	33	**12**(36.4%)	58	**7**(12.1%)	**.01**
General Fatigue	33	**11**(33.3%)	58	**10**(17.2%)	.12
Sleep-Rest Fatigue	33	**10**(30.3%)	58	**7**(11.9%)	.05
Cognitive Fatigue	33	**8**(24.2%)	58	**8**(13.8 %)	.26

Abbreviations: POMS: pediatic-onset multiple sclerosis; HC: healthy control
Note. Severe fatigue was defined as scores falling two or more standard deviations from published norms (Varni et al., 2010);
†Parent-rated fatigue data not available for 2 patients and 25 HCs; †Self-rated fatigue data not available for 7 HCs

Aim 1: Group Differences in CPT Performance

Outcomes on the CPT and the Finger-Tapping Task are presented in Table 6. Groups did not significantly differ on the Finger-Tapping Task (p=.15). As such, we did not control for simple motor speed on subsequent IIV analyses.

Controlling for covariates, POMS participants showed more variable performance than HCs on the CPT using both overall ISD (p=.01) and COV (p=.001); these findings were consistent collapsing across blocks and within each block (all p values $\leq$.01; see bar graph presented as Figure 8).

Comparing across blocks, ISD significantly increased on the second (i.e., letter) block relative to the first (i.e., number) block for both POMS (t=3.32, df=34, p=.002) and HCs (t=4.22, df=69, p<.001). Though COV increased between blocks for POMS, the difference was not statistically significant (t=1.94, df=34, p=.06) whereas HCs were significantly more variable on the second half (t=3.17, df=69, p=.002) using COV. There was no group by block interaction (i.e., ISD (t=-0.31, df=67.27, p=.76); COV (t=-0.15, df=55.98, p=.88) (see Figures 9a and 9b).

Accuracy and mean response time were examined to contextualize the IIV findings and are included in Table 6. Controlling for covariates, the POMS group was significantly less accurate (p=.02), less able to discriminate between signal and noise (p=.01) and made more errors of omission (p=.02) and perseverative errors (p=.01) relative to HCs. Groups did not differ significantly on mean response time (p=.44). Overall, our hypotheses were supported. That is, POMS demonstrated greater IIV and reduced accuracy relative to HCs on the CPT.

An additional finding was that better accuracy showed a statistically significant association with faster response speed among HCs (r=-.36, p=.003) but not POMS participants (r=-.20, p=.24).

POMS and HC groups were fairly well matched on commission errors (on average 6.8 in POMS vs. 5.1 in HCs), though the between-group diffence approached significance (p=.06). As such, including all trials where a response was given (i.e., correct trials and commission errors), provided a more comprehensive view of variability, capturing lapses in focus or impulsivity that might not be evident if only correct trials are analyzed. Recognizing that IIV could also be derived using only correct trials, as done in prior work (e.g., Wojtowicz, Berrigan, & Fisk, 2012), analyses were re-run in a sensitivity analysis using only correct trials. Using only correct trials, results were broadly consistent with those including commission errors (Supplemental Tables C).

As well, given group differences in omission rates, we imputed the maximum time (i.e., 1000 ms) for trials where no response was given and re-ran the data in a sensitivity analysis. The pattern of findings were unchanged (Supplemental Table D). We also looked qualitatively to assess whether responses following an omission error were given in under 200 milliseconds (i.e., a "perseverative error" as labeled by a task). If observed, which we did not, this may have reflected a carryover from the missed trial given that it is not possible to perceive a stimulus that quickly.

Table 6. Group differences (POMS-HC) in primary CPT outcomes from the multiple linear regression presented as estimated marginal means (robust modelling)

Outcome	**POMS (n=34)** M(SE)	**HC (n=63)** M(SE)	B(SE)	*p*	**95% Confidence Interval for effect estimate** Lower	Upper	Multiple R^2
Finger Tapping Dominant Hand (raw score)[a]	56.90 (1.09)	58.90 (0.80)	-1.98 (1.38)	.15	-4.63	0.67	.18
IIV (ISD; ms)[a]	116.70 (5.20)	99.10 (3.81)	17.57 (6.89)	**.01**	4.91	30.23	.19
IIV (COV; %)[a]	20.60 (0.79)	17.30 (0.58)	3.36 (1.02)	**.001**	1.45	5.27	.20
Accuracy (% correct)[a]	90.90 (1.27)	94.60 (0.93)	-3.70 (1.61)	**.02**	-6.80	-0.60	.23
Mean RT (ms)[a]	561.00 (8.66)	569.00 (6.34)	-8.68 (11.11)	.44	-29.74	12.38	.13
Detectability (d')[a]	3.10 (0.12)	3.50 (0.09)	-0.40 (0.15)	**.01**	-0.71	-0.11	.28
Omissions[a]	5.49 (0.76)	3.27 (0.56)	2.22 (0.97)	**.02**	0.36	4.08	.23
Commissions[a]	6.80 (0.75)	5.07 (0.55)	1.73 (0.92)	.06	-0.10	3.56	.20
Perseverations[a]	0.58 (0.12)	0.14 (0.08)	0.44 (0.16)	**.01**	0.16	0.72	.16

Abbreviations: COV: coefficient of variation; CPT: Continuous Performance Test; HC: healthy control; IIV: intra-individual variability; ISD: individual standard deviation; POMS: pediatric-onset multiple sclerosis; RT: response time
[a]controlling for age, sex, and parental education
Note. Sample sizes are reduced due to missing parental education data for one patient and seven HCs. RT is measured in milliseconds

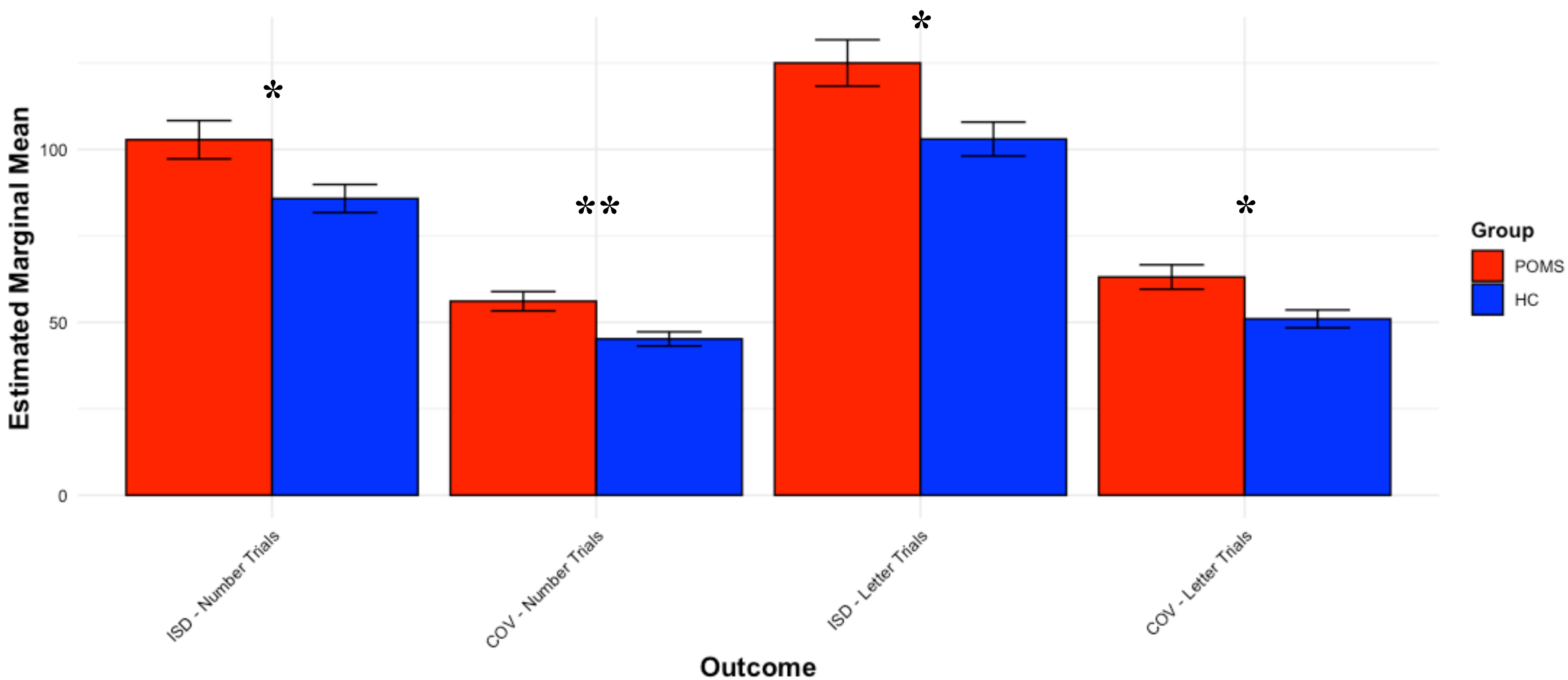

Figure 8. *Group differences in IIV across CPT blocks (Numbers versus Letters)*

Note. *p= .01; **p<.005

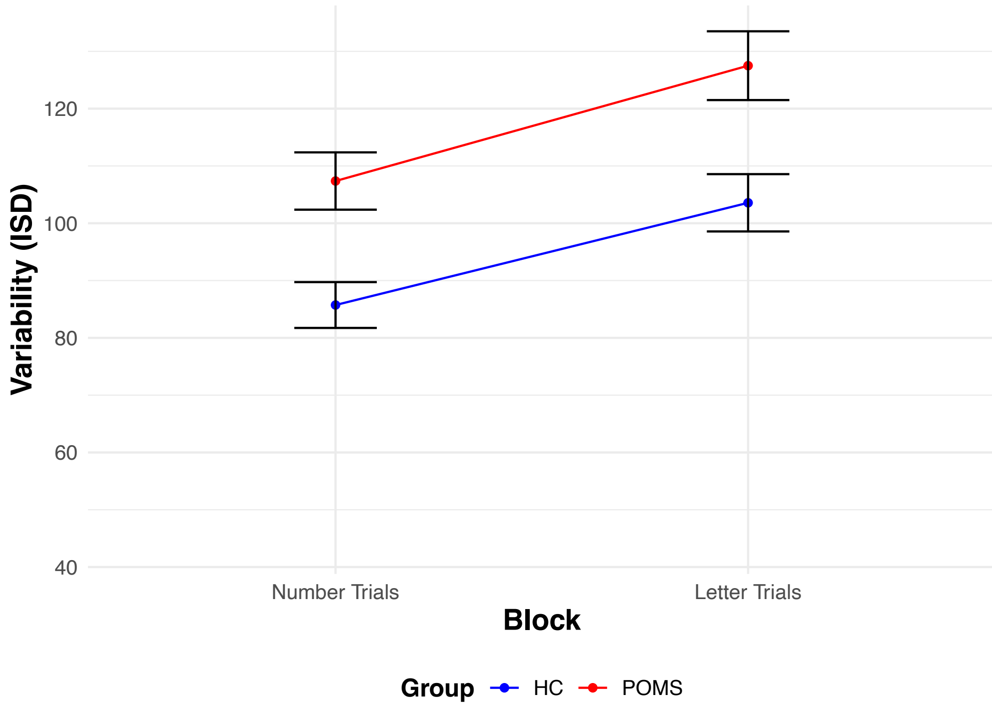

Figure 9a. *Mean ISD for POMS participants and HCs by block*

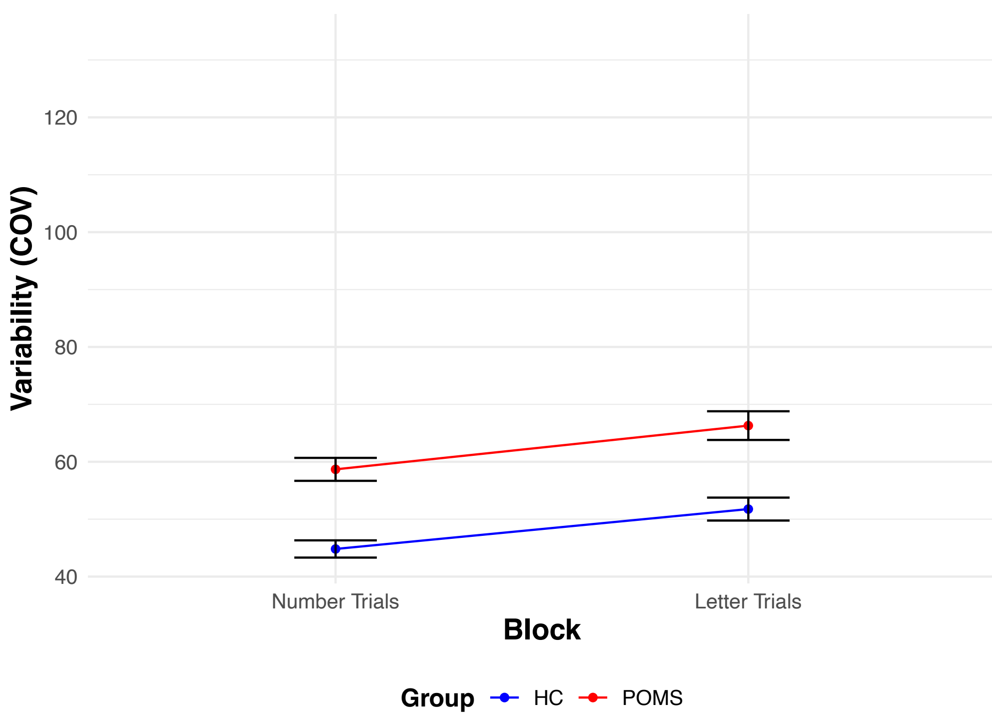

Figure 9b. *Mean COV for POMS participants and HCs by block*

Aim 2: Associations Between Subjective Fatigue and Cognitive Fatigability

Given the finding that POMS were not more variable over time relative to the HCs (i.e., no group by block interaction), trials across the task (versus the first or second half only) were used for correlational analyses.

In general, parent- and self-rated symptoms of fatigue did not significantly associate with IIV when collapsed across groups or within each group (Table 7). While not meeting the threshold for statistical significance, a paradoxical finding was observed in the POMS group; higher self-reported sleep-rest fatigue scores (i.e. indicative of *less* fatigue) were moderately associated with greater ISD (r_s=.45, p=.01) and COV (r_s=.42, p=.01). Positive associations were also observed in the secondary analyses. Specifically, participants with POMS who reported higher self-reported sleep-rest fatigue scores (i.e. indicative of *less* fatigue) showed longer (i.e. slower) mean response time (r_s=.51, p<.01) and the strength of this relationship was strong for POMS. Of note, these correlations were around zero for HCs (values presented in Table 7).

Table 7. Spearman correlations (two-tailed) between subjective fatigue and CPT outcomes

CPT Outcome	Group	n	Total Fatigue	General Fatigue	Sleep-Rest Fatigue	Cognitive Fatigue
			Correlations			
			Parent-rated			
ISD	All	70	r_s=.01, *p*=.96	r_s=-.01, *p*=.94	r_s=.10, *p*=.42	r_s=-.10, *p*=.39
	POMS	28	r_s=.08, *p*=.68	r_s=-.00, *p*=.99	r_s=.10, *p*=.62	r_s=-.04, *p*=.84
	HC	42	r_s=.05, *p*=.74	r_s=.12, *p*=.45	r_s=.22, *p*=.16	r_s=-.08, *p*=.60
COV	All	70	r_s=.01, *p*=.93	r_s=.01, *p*=.94	r_s=.09, *p*=.45	r_s=-.09, *p*=.44
	POMS	28	r_s=.06, *p*=.75	r_s=-.00, *p*=.99	r_s=.10, *p*=.60	r_s=-.10, *p*=.60
	HC	42	r_s=.10, *p*=.52	r_s=.18, *p*=.26	r_s=.24, *p*=.12	r_s=-.02, *p*=.88
Mean RT	All	70	r_s=-.02, *p*=.88	r_s=-.05, *p*=.65	r_s=.09, *p*=.43	r_s=-.08, *p*=.49
	POMS	28	r_s=.04, *p*=.83	r_s=-.07, *p*=.71	r_s=.07, *p*=.71	r_s=.04, *p*=.83
	HC	42	r_s=-.06, *p*=.70	r_s=-.06, *p*=.70	r_s=.13, *p*=.40	r_s=-.17, *p*=.27
Accuracy (% correct)	All	70	r_s=.09, *p*=.44	r_s=.05, *p*=.68	r_s=.06, *p*=.62	r_s=.12, *p*=.31
	POMS	28	r_s=-.05, *p*=.78	r_s=-.04, *p*=.85	r_s=-.12, *p*=.53	r_s=.09, *p*=.67
	HC	42	r_s=.04, *p*=.82	r_s=-.07, *p*=.67	r_s=.04, *p*=.80	r_s=.04, *p*=.79
			Self-rated			
ISD	All	91	r_s=.20, *p*=.06	r_s=.21, *p*=.05	r_s=.18, *p*=.09	r_s=.13, *p*=.24
	POMS	33	r_s=.38, *p*=.03	r_s=.35, *p*=.05	r_s=.45, *p*=.01	r_s=.20, *p*=.27
	HC	58	r_s=.07, *p*=.58	r_s=.12, *p*=.36	r_s=-.01, *p*=.92	r_s=.07, *p*=.63
COV	All	91	r_s=.16, *p*=.12	r_s=.17, *p*=.10	r_s=.15, *p*=.17	r_s=.10, *p*=.33
	POMS	33	r_s=.33, *p*=.06	r_s=.28, *p*=.11	r_s=.42, *p*=.01	r_s=.15, *p*=.40
	HC	58	r_s=.06, *p*=.64	r_s=.11, *p*=.43	r_s=-.01, *p*=.90	r_s=.06, *p*=.66
Mean RT	All	91	r_s=.18, *p*=.08	r_s=.19, *p*=.06	r_s=.19, *p*=.08	r_s=.13, *p*=.20
	POMS	33	r_s=.37, *p*=.03	r_s=.31, *p*=.08	**r_s=.51, *p*<.01**	r_s=.25, *p*=.16
	HC	58	r_s=.06, *p*=.60	r_s=.12, *p*=.35	r_s=-.01, *p*=.93	r_s=.06, *p*=.64
Accuracy (% correct)	All	91	r_s=.06, *p*=.60	r_s=.10, *p*=.33	r_s=.02, *p*=.87	r_s=.04, *p*=.74
	POMS	33	r_s=-.01, *p*=.96	r_s=.02, *p*=.93	r_s=-.02, *p*=.92	r_s=-.03, *p*=.87
	HC	58	r_s=.09, *p*=.46	r_s=.15, *p*=.26	r_s=.02, *p*=.90	r_s=.08, *p*=.57

Abbreviations: COV: coefficient of variation; CPT: Continuous Performance Test; HC: healthy control; ISD: individual standard deviation; POMS: pediatric-onset multiple sclerosis; RT: response time

Aim 3: Brain-Behaviour Associations

POMS participants demonstrated lower whole brain FA (0.188 ± 0.00 versus 0.194 ± 0.00), p<.001) relative to HCs. Group differences in MD, AD, and RD can be found in Supplemental Table E.

Though most assumptions underlying linear regression were met, there were slight deviations in homogeneity of variance and normality of residuals observed. As such, robust estimation, specifically sandwich estimation was utilized to yield more reliable standard errors and consequently, also p values. Despite not reaching the threshold for statistical significance, the relationship between whole brain FA and IIV in POMS was in the expected direction (Tables 8-9). Associations between FA and cognition were driven by lower levels of FA, thus stronger relationships were observed for the POMS group, as expected whereby higher FA was associated with reduced IIV.

The same pattern of findings was observed for the secondary cognitive outcomes (i.e., higher FA associating with better accuracy and slower (perhaps less impulsive) mean response time). Relationships by group are visualized in Figures 10a-d.

Supplemental data including brain-behaviour models with MD, AD, and RD are presented in Supplemental Table F (POMS) and Supplemental Table G (HC). The results were consistent with those found with FA, though the values of MD, RD and AD are inverse to FA. As such, higher MD, RD, and AD, indicative of reduced white matter integrity, myelin content and neuropathology, and axonal degeneration respectively, associated with greater IIV, reduced accuracy, and slower response time on the CPT for patients.

Of note, results were unchanged in sensitivity analyses which excluded one HC and two MS participants who underwent an MRI scan more than three months following the cognitive evaluation (data not shown for brevity).

Table 8. Whole brain white matter FA as a correlate of CPT fatigability, accuracy, and mean response time in POMS patients (robust modelling)

DTI Metric	POMS (n=30) B(SE)	p	95% Confidence Interval for effect estimate Lower	Upper	Multiple R^2
Whole Brain FA (0 – 1)					
IIV: ISD	-10.51 (12.35)	.40	-29.46	8.44	.17
IIV: COV (%)	-1.56 (1.83)	.40	-4.34	1.23	.18
Accuracy (% correct)	2.30 (2.32)	.33	-2.26	6.86	.28
Mean RT	-7.31 (14.47)	.62	-34.12	19.49	.08

Abbreviations: COV: coefficient of variation; CPT: Continuous Performance Test; ISD: individual standard deviation; POMS: pediatric-onset multiple sclerosis; RT: response time
Note. Models were adjusted for age, sex, and parental education. Beta values were adjusted (i.e., divided by 100) to represent a 0.01 increase in FA.

Table 9. Whole brain white matter FA as a correlate of CPT fatigability, accuracy, and mean response time in HCs (robust modelling)

DTI Metric	HC (n=51) B(SE)	p	95% Confidence Interval for effect estimate Lower	Upper	Multiple R^2
Whole Brain FA (0 – 1)					
IIV: ISD	0.70 (6.88)	.92	-10.92	0.01	.18
IIV: COV (%)	0.28 (1.12)	.80	-1.53	2.10	.11
Accuracy (% correct)	2.42 (1.30)	.07	0.41	5.24	.12
Mean RT	-6.20 (10.96)	.57	-30.54	18.14	.18

Abbreviations: COV: coefficient of variation; CPT: Continuous Performance Test; HC: healthy control; ISD: individual standard deviation; RT: response time
Note. Models were adjusted for age, sex, and parental education

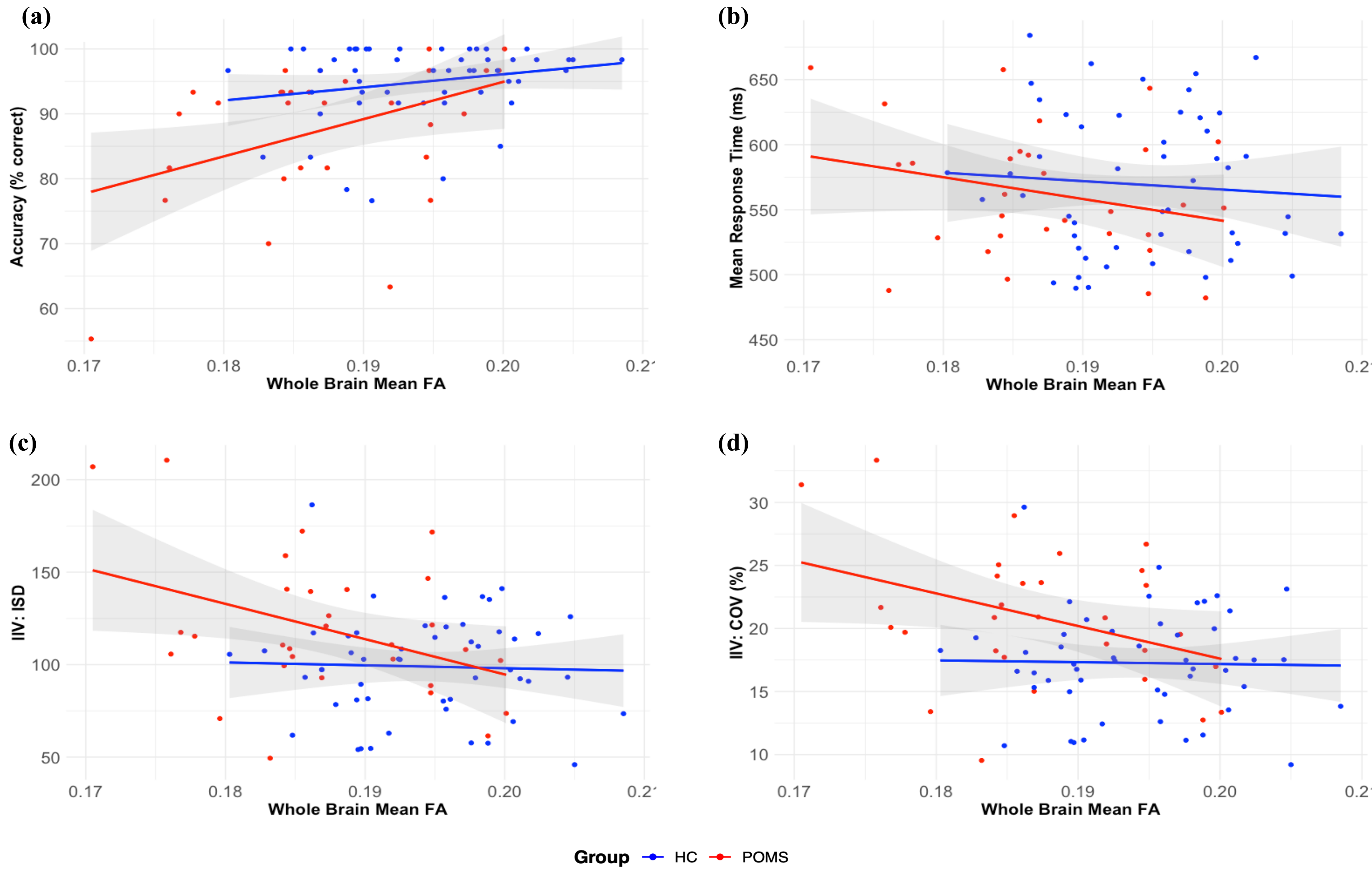

Figure 10a-d. *Associations between whole brain FA and (a) accuracy, (b) Mean RT, (c) ISD, and (d) COV in POMS and HCs*

Discussion

The experience of fatigue is common affecting approximately 15-30% of the general adolescent population, though fatigue is even more common and severe in POMS (Carroll et al., 2016; Findlay, 2008; Kluger, Krupp, & Enoka, 2013). Consistent with the literature, we found that endorsement of severe symptoms of fatigue was three times higher in POMS compared to HCs for both parent- (42.9% vs. 14.3%) and self-report (36.4% vs. 12.1%).

In addition to reporting higher levels of subjective fatigue, POMS participants also demonstrated greater IIV and poorer accuracy on a performance-based test, but not slower response time. Indeed, IIV has been more sensitive than mean response time in differentiating adults with MS and controls on measures such as the Paced Auditory Serial Addition Test (PASAT) (Mazerolle et al., 2013; Wojtowicz, Berrigan, & Fisk, 2012). A strength of this work is that possible confounds impacting the measurement of subjective fatigue (i.e., mood) and IIV (i.e., simple motor speed) could be ruled out because groups were matched on these outcomes, permitting greater confidence that the observed group differences are unlikely to reflect these factors.

Given the novelty of looking at IIV in POMS, two approaches were used – ISD and COV. ISD indicates how much an individual deviates from their mean and is quantified in the same units (e.g., milliseconds) as the original data. COV is standardized as a percentage, normalizing within subject variability in relation to a participant’s mean. While both provide important information, raw ISD (as used in the present study) may be considered more crude relative to COV. In support of this, while both ISD and COV were sensitive to detecting group differences in response time performance across the CPT, COV appeared to be slightly more sensitive in group comparisons. Of note, studies that have calculated residualized ISD that controls for relevant influences such as practice and learning effects (Wojtowicz, Berrigan, & Fisk, 2012) argue that it is more sensitive compared to COV; it would be of great interest to use the residualized approach in future studies that may look at IIV across tasks in the PCNB (Roalf et al., 2014). Utilizing a longer task in future work as well as parsing out individual factors (e.g., reserve, insight, effort, etc.) may provide us with more information about fatigability and compensation in this population. This is elaborated on below.

While slow response time is a common finding in POMS and specifically within the cohort included in this study (Barlow-Krelina et al., 2021), perhaps the finding that the controls were not significantly faster than patients on the CPT suggests that the POMS patients had more difficulty with attentional inhibitory control and approached this task more impulsively. Specifically, POMS participants appear to have failed to strategize by reducing their speed of responding to improve their response accuracy and were also more variable in their response time than controls who may have appropriately adjusted their response speed to better process the targets.

We did not observe an association between IIV, accuracy, or mean response time on the CPT and subjective levels of total, cognitive, or general fatigue. Perhaps a counterintuitive finding was that most of the associations (though not statistically significant) were positive (and opposite to our hypothesis), indicating that higher scores on the PedsQL-MFS indicative of less fatigue associated with greater IIV. There were also differences in the strength of the associations between the POMS and HC groups, particularly for self-reported fatigue. Specifically, the POMS group showed somewhat stronger, positive associations, though still not statistically significant. Accordingly, self-parent discrepancy scores were calculated and used to examine whether patients may have had poor insight/meta-awareness into their fatigue. Findings regarding this association in the literature are heterogeneous (Aldughmi, Bruce, & Siengsukon, 2017; Bruce, Bruce, & Arnett, 2010; Cehelyk et al., 2018; Diamond et al., 2008; Mackay et al., 2021; Morrow et al., 2009; Walker et al., 2012).

Other factors that may underlie the paradoxical finding that better quality of life (i.e., less reported problems with fatigue) associated with greater variability on the CPT include executive control, effort, and motivation. While some individuals may feel less fatigued, their executive control systems may still be taxed, leading to greater response time inconsistency, particularly when sustained attention is required. Alternately, one should consider interpretation of questionnaire items. For example, some individuals who *sleep, nap, or rest a lot* may not perceive this behavior as problematic. Rather, they might view it as a protective strategy, preventing them from becoming overtaxed or exhausted. As a result, they may rate fewer problems with items of this nature on the PedsQL-MFS (Varni et al., 2022). Despite this, they may still experience issues with cognitive control, as seen through greater IIV on tasks like the CPT.

It is also plausible that individuals who perceive themselves as less fatigued may be relying on compensatory strategies, such as working in bursts of high effort followed by periods of disengagement, leading to greater variability and slower response time as the individual tries to gain control. This strategy-driven approach does not serve someone well on a task like the CPT as better accuracy was not observed among those who reported less fatigue.

Next, differences in fatigue tolerance may contribute to the patterns observed in the data. For example, some individuals may have a higher tolerance for fatigue or be better at masking it, reporting lower perceived fatigue despite experiencing cognitive strain which can be challenging to pinpoint relative to physical strain for example.

Including measures of effort/motivation is likely of utility when studying complex phenomenon such as fatigue, as in addition to declining resources, lack of motivation is one theory that has been postulated to explain cognitive fatigue (Herlambang, Cnossen, & Taatgen, 2021). Of note, the frontally mediated functions described above along with issues of motivation and effort are considered as “psychological factors” in the taxonomy by Kluger, Krupp, & Enoka (2013).

Regarding the final study aim, lower whole brain white matter integrity was not significantly associated with IIV on the CPT, though trends were in the expected direction, especially for the POMS group for whom white matter integrity was significantly reduced. These findings are consistent with prior reports showing a functional impact of loss of tissue integrity on information processing (Akbar et al., 2016; Bethune et al., 2011). As well, researchers have postulated that behaviourally, IIV may manifest due to neural noise and altered neuronal firing associated with loss of white matter integrity (Mazerolle et al., 2013). While much remains unknown regarding neurological correlates of response slowing versus IIV, it has been suggested that IIV may be more sensitive to white matter integrity. Our pattern of findings regarding IIV and mean response time fit with this theory (Mazerolle et al., 2013).

Limitations and Future Directions

In addition to the considerations presented above, it is possible that the use of trait versus state fatigue influenced the findings regarding the association between CPT performance and parent- and self-reported fatigue given that they are not necessarily temporally matched (Aldughmi, Bruce, & Siengsukon, 2017). As well, measures like the PedsQL-MFS (Varni et al., 2002), may be influenced by or may capture emotional distress as symptoms of depression can include low energy and feeling tired (Parrish et al., 2013). This bias has also been identified with other standardized measures in adult samples, such as the Behavior Rating Inventory of Executive Function (Shwartz et al., 2020). However, as mentioned, the finding that groups in this study did not differ on emotional distress suggests that the observed difference in fatigue is unlikely to reflect mood related differences.

Our study also used the cutoff of two SDs (MacAllister et al., 2009) to define severe fatigue. While this was deemed to be an ideal way of parceling the data given that more mild fatigue seems to be typical among healthy youth (Findlay, 2008), it was somewhat arbitrary.

IIV in reaction time has been suggested as a behavioural marker of fatigue and attention problems (Aldughmi, Bruce, & Siengsukon, 2017; Bruce, Bruce, & Arnett, 2010), and the association between IIV and white matter microstructure has been documented in healthy children (Wiker et al., 2023). The use of a whole brain DTI measure in our work may have lacked the specificity required to identify statistically significant relationships with IIV. As well, while global MRI metrics like total brain volume and lesion volume are correlated with processing speed (Till et al., 2011), while brain white matter diffusion metrics may not be sensitive to the pathways that subserve attentional control. Future work may wish to look at FA of the corpus callosum, responsible for interhemispheric information transmission (Akbar et al., 2016; Todorow et al., 2014), white matter microstructural organization in the default mode network (DMN) tracts, and in the cingulum bundle, regions and frontal networks shown to be implicated in attention and information processing speed (Connaughton et al., 2022).

In addition, functional imaging studies have the potential to elucidate biological correlates of variability (Kriger & Sumowski, 2020). For example, Esterman and colleagues (2013) have utilized their own version of a CPT. They demonstrated two attentional states, namely a less error-prone state ("in the zone"), marked by greater recruitment of the DMN, and a more effortful state ("out of the zone"), characterized by less optimal sustained performance relying on dorsal attention network regions.

Building on Akbar and colleagues (2015) findings linking increased activation in various brain regions to faster response times in POMS and considering Esterman et al.'s (2013) concepts, it may be of interest to employ functional imaging techniques to explore how alterations in brain connectivity, particularly heightened activation within the DMN and frontal attentional networks, may facilitate individuals staying "in the zone". By examining brain activation patterns, we can better elucidate whether compensatory strategies may maintain cognitive performance despite structural abnormalities, thereby explaining the observed variability in cognitively demanding sustained attention tasks like the CPT.

To our knowledge, this study represents the first investigation of IIV in POMS. Though IIV differed between groups on the CPT, future research may wish to utilize different cognitive outcomes than the CPT employed in this work. This is because the CPT is a time-constrained measure whereby each person has a finite (i.e., one second) window to respond in a forced-choice design. As such, if an individual misses the response window, they would be making an error of omission (which was higher among POMS participants in this study).

Researchers of future studies may also aim to assess IIV in other cognitive domains outside of attention (e.g., information processing speed on the PASAT) as well to better understand this generalizability of our findings on the CPT.

Unfortunately, POMS is characterized by high MRI disease burden, depression, fatigue, and cognitive impairment which progressively worsen (Yeh, 2016). By understanding the interplay of these factors, we will increase our knowledge to hopefully reverse the trajectory.

Chapter 4: General Discussion

Introduction

Despite its profound impact on many facets of daily living for individuals with multiple sclerosis (MS), fatigue remains poorly understood. The taxonomies by Kluger, Krupp, & Enoka (2013) and Linnhoff and colleagues (2019) were developed with the goal of enhancing the study and reporting of fatigue and fatigability in clinical groups including MS. These complementary taxonomies highlight a move towards a more holistic approach to fatigue assessment and management and were used to ground this dissertation research across two studies.

Summary of Studies and Alignment of Findings with the MS Literature

Chapter 2 consisted of a systematic review examining the relationship between fatigue and cognition in pediatric-onset multiple sclerosis (POMS). The goal of this review was to incorporate newer evidence and quantitively summarize the results using meta-analysis. However, due to heterogeneity in the methodologies used and the small number of studies that met inclusion criteria, the data were qualitatively summarized, and an exploratory meta-analysis was presented instead.

The narrative synthesis suggested that while total fatigue is not reliably associated with overall cognitive functioning, there may be statistically significant, albeit weak, associations between fatigue and specific cognitive domains. This was particularly apparent for performance-based and subjectively reported executive functioning and sustained attention. Results of the supplemental meta-analyses were generally consistent with the narrative synthesis, though as noted, quantitative analyses were limited by the dearth of independent studies that could be included in this analysis.

A greater understanding of the complexities of assessing fatigue was garnered through the review. Insights regarding how to best address these complexities are described below. As well, there was an identified need for researchers to direct their efforts towards the study of fatigability.

Therefore, the primary aim of Chapter 3 was to assess whether individuals with POMS differed in intra-individual variability (IIV; a proxy of fatigability) relative to matched healthy controls (HCs). It is believed that this was the first study to examine IIV in POMS. IIV in response time was assessed using a three-minute version of the Continuous Performance Test (CPT). In addition, the prevalence of parent- and self-reported fatigue in POMS was characterized using the Pediatric Quality of Life Inventory™ Multidimensional Fatigue Scale (PedsQL-MFS; Varni et al., 2002). The respective associations between subjective fatigue and fatigability (i.e. IIV) were assessed and contextualized by comparing against the observed associations between fatigue and traditional measures on the CPT (i.e., accuracy, and mean response).

Severe total fatigue was endorsed about three times more in the POMS group by both parents (42.9%) and patients (36.4%) relative to HCs. These figures are comparable to prior research in this population (Carroll et al., 2016). In support of the hypotheses, results showed that POMS participants were more variable than HCs using both individual standard deviation (ISD) and coefficient of variation (COV) as indices of IIV. Further, IIV was higher for POMS looking across the task, though IIV was also higher for HCs as the task went on.

One interpretation of this finding is that IIV may be a reflection of neural integrity in POMS. For HCs, the decrease in performance may be a temporal reflection of reduced vigilance (Al-Shargie et al., 2019), possibly also boredom or mind-wandering. In the absence of counterbalancing the number and letter blocks presented on the CPT version used, it cannot be concluded that the effect is solely due to time; task demand and stimuli utilized should also be considered. For example, participants may be more familiar with seeing numbers on a digital clock than the presentation of letters in the version of the CPT used.

Though the CPT used in this dissertation was sensitive to detecting group differences in IIV, behaviourally, one may also wish to examine IIV using tasks other than the CPT. It may also be of interest to look at dispersion in accuracy and response time across a longer battery or variability in attentional states across blocks of a longer task such as the Conners CPT. The Conners CPT also has a higher cognitive loading with changes in the inter-stimulus interval.

The POMS group was significantly less accurate, less able to discriminate between signal and noise, and made more errors of commission and perseverations relative to HCs after controlling for relevant covariates. Notably, groups did not differ on the cruder metric of mean response time, suggesting that IIV may be a more nuanced way to look at response time performance across a task; at least on a task such as the CPT with time-constrained response windows. A prior study on this cohort of patients (Barlow-Krelina et al., 2021) showed that accuracy was more sensitive than response time. While this finding may be surprising given that slowed processing speed is considered one of the earliest and hallmark cognitive changes in MS, it helps to contextualize the present findings.

Furthermore, researchers have suggested that in comparison to mean response time and accuracy, IIV is more sensitive in differentiating adults with MS (AOMS) and HCs on measures such as the Paced Auditory Serial Addition Task (PASAT) (Mazerolle et al., 2013; Wojtowicz et al., 2012). The finding that HCs were not significantly faster than POMS participants in the present study may also indicate that POMS participants had more difficulty with attentional inhibitory control and processing efficiency. Accurate performance was also significantly associated with slower response speed among HCs but not POMS participants. This suggests that HCs were able to appropriately adjust their response speed to better process the targets than the POMS group overall. Further, the finding of inefficient or reduced attentional control fits with the conceptual and operational definitions of cognitive fatigue (Holtzer et al., 2011).

In previous research by Aldughmi, Bruce, & Siengsukon (2017), only response speed inconsistency measured using hit reaction time standard deviation score on the CPT, and not grip strength or the 6 Minute Walk Test, significantly associated with subjective report of physical and cognitive fatigue. In this dissertation, most of the associations between parent- or self-ratings of subjective fatigue were not associated with IIV. There was one exception whereby *fewer* self-reported sleep-rest fatigue symptoms (i.e., higher score on the questionnaire) associated with *greater* IIV and slower mean response time for POMS participants.

It is possible that subjective trait fatigue in POMS may not map onto in-vivo behavioural measures. Performance fatigability is state-dependent by definition (Linnhoff et al., 2019). Therefore, to understand whether IIV is a behavioural marker of fatigue (or proxy for fatigability), researchers should utilize measures of state versus trait fatigue in future correlational research designs. One may also wish to look at fatigability using a within-subject repeated measures design as some studies have done (e.g., assessing IIV before and after a fatiguing measure or assessment battery) (Barrios et al., 2022).

Neurologically, IIV may capture neural noise and reduced white matter integrity (Mazerolle et al., 2013). In Chapter 3, white matter integrity, namely whole brain fractional anisotropy (FA), was examined as a correlate of increased IIV in POMS. First, consistent with the POMS literature, participants demonstrated lower whole brain FA relative to HCs (Akbar, et al., 2016; Blaschek et al., 2013; Vishwas et al., 2010). Though IIV is known to be associated with decreased white matter integrity in healthy adults and in AOMS (Mazerolle et al., 2013), examining the association between IIV and white matter integrity in POMS was novel.

While generally in the expected direction, white matter integrity was not significantly associated with IIV, accuracy, or response time on the CPT. Despite not reaching the set conservative threshold for statistical significance, the observed pattern of findings is supported by overlapping regions involved in both attentional processing and the fatigue circuit (Linnhoff et al., 2019). The fatigue circuit, or network involving cortical, striatal, and thalamic regions, and the corpus callosum, has been identified and is illustrated in Figure 11 (Ayache & Chalah, 2017; Linnhoff et al., 2019).

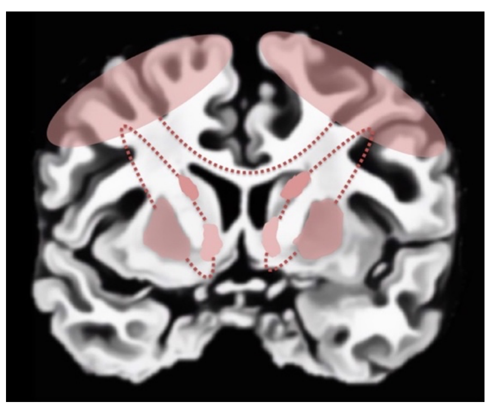

Figure 11. *Ayache & Chalah's illustration of the fatigue loop (Ayache & Chalah, 2017)*

Limitations and Future Directions

Regarding the study of fatigability, we acknowledge the relatively small sample size, particularly for brain-behaviour analyses. This may have reduced the required statistical power to detect significant relationships. However, this is the nature of studying a rare disease. Further, our cross-sectional study design (repeated measures also not utilized) did not permit us to make causal statements.

While whole brain diffusion data was utilized in this dissertation given the investigation of a novel outcome (i.e., IIV) in POMS, future research should take an a-priori approach to identifying regions or networks (Pardini et al., 2010) when probing this brain-behaviour association. Previous studies in AOMS have demonstrated relationships between self-reported fatigue and fatigability (e.g., IIV) with structural and functional abnormalities in frontal and parietal regions. White matter microstructural organization in the default mode network tracts, anterior thalamic tracts, the corpus callosum, and in the cingulum bundle (Bester et al., 2013; Connaughton et al., 2022) has also been identified as a correlate of fatigability (Linnhoff et al., 2016).

Finally, the relationship between subjective fatigue and damage to white matter tracts was not investigated in the present research. However, this association with white matter tracts in the prefrontal cortex has been replicated across several studies in AOMS (Bisecco et al., 2016; Pardini et al., 2010; Rocca et al., 2014) and is worthy of future study in POMS.

Clinical Implications

In MS, fatigue can occur as a primary consequence of changes in the central nervous system, or it may arise secondary to other symptoms (e.g., pain, sleep disturbance, depression, etc.). Alternatively, fatigue may represent its own diagnosis as in the case of chronic fatigue syndrome (more formally known as myalgic encephalomyelitis) and can be considered a comorbidity of neurological disease (Penner & Paul, 2017). Fatigue has been understudied in many clinical populations, but especially in POMS, beyond identifying that it is a common and functionally impairing experience.

Recently, researchers have become interested in studying fatigue in conditions like long-COVID, and in individuals experiencing persistent concussion symptoms. Mechanistically, these conditions have been associated with neuroinflammation (including inflammation that is chronic and low-grade) and therefore have commonalities with MS. In fact, fatigue is among the most common symptom reported by youth with persistent concussion and individuals with long-COVID (Gross et al., 2023). Learnings from one population have the potential to inform others and for many reasons, we must continue to strive to understand fatigue and its implications in POMS. One reason is that the prevalence of POMS appears to be increasing.

Specifically, a 2024 population-based study led by prominent Canadian MS researcher Helen Tremlett, found that the POMS prevalence per 100,000 increased from 2.93 to 4.07 between 2003 and 2019 in the province of Ontario. Combined, British Columbia and Ontario represent more than 50 percent of Canada's POMS population.

Moreover, the proportion of children who need to repeat a grade in school after MS onset (i.e., first attack) can be as high as 50 percent in POMS patients, especially those who had their disease onset after 11 years of age (Mikaeloff et al., 2010). Fatigue may exacerbate academic difficulties by keeping kids out of school or may impact their attention and learning. Fatigue may also reduce opportunities for socialization with psychosocial implications. This may feed into a cycle that also involves mental health sequelae.

Until recently, fatigue was solely assessed using subjective report, either qualitatively or on a standardized questionnaire. However, like other experiences (e.g., pain), self-report is susceptible to personal biases and individual differences in tolerance. Issues of insight, particularly in children and youth, are also important to consider. Tangentially related, the intra-class correlation coefficients for parent-self report was lowest for cognitive fatigue which is fitting given that it can be harder to observe cognitive relative to physical and sleep-rest fatigue.

An observation from the systematic review was that researchers do not always use age-appropriate, validated tools for the assessment of subjective fatigue and there lacks a gold standard measure of fatigue. In the current dissertation, the PedsQL-MFS (Varni et al., 2002) was utilized. It is also notable that this measure has shown more consistent relationships with fatigability relative to others used in the literature.

Taxonomies provided by Kluger, Krupp, & Enoka (2013) and Linnhoff et al., (2019) indicate the complex and multifaceted nature of fatigue, including that its fluid and perhaps state-dependent. As such, in addition to using validated fatigue questionnaires, measures of trait fatigue may also be needed. Also aligned with the taxonomies, future research should be designed to integrate measures that capture subjective fatigue and objective (both cognitive and physiological) fatigability.

Valid and reliable cognitive measures should be also be used in research and clinically (e.g., CPT, Trail Making Test, PASAT, Symbol Digit Modalities Test) and relevant potential confounds (e.g., mood, motor) considered.

In addition to behavioural measures, biomarkers (e.g., inflammatory cytokines in the cerebrospinal fluid) may be of utility to better understand what fatigue is and if there are causal mechanisms. In a research context, it may also be of interest to utilize other imaging techniques. This can include Neurite Orientation Dispersion and Density Imaging which can offer novel insights into microstructural features of white matter change (Preziosa et al., 2023). Less invasive electrophysiological techniques that align with the fatigue taxonomies (e.g., in-vivo EEG, heart rate variability) can also be utilized to increase our understanding and guide treatment. Clinically, however, the use of imaging in fatigue specific assessment may not be required; it can be more helpful at the group level as we continue to explore the biological bases of fatigue. As well, timing of imaging is important (e.g., around a presumed attack) or as we learn more from needed longitudinal studies as to whether inflammation onset provokes fatigue symptoms.

Specifically in clinical neuropsychology, the impact of fatigue in psychological assessment (e.g., test batteries, score and profile interpretation), and in clinical formulation is most important to consider. For example, being able to understand whether performance reflects motor impairment and/or fatigability, mood, or other variables. Imaging alone does not provide us with this information.

Furthermore, the use of digital assessments may enhance the measurement of IIV in the clinical setting. As noted previously, IIV may be better able to detect subtle changes that may be missed when looking at mean-based outcomes. Capturing these nuances is also important for clinicians to be able to generalize findings and to develop more targeted interventions.

A client-centered approach to care is always integral to good practice, even more so in a heterogeneous population such as POMS. Helping an individual and their family identify functional goals is paramount. Appropriate recommendations may include strategies such as pacing to prevent fatigue - both physical and cognitive, building in extra time for breaks in the daily schedule, and reducing multi-tasking. Given the strong associations between mental health and the experience of fatigue, it is also important to help individuals navigate appropriate mental health supports. Strategies may include behavioural activation and locating and encouraging opportunities for social engagement, as tolerated.

Closing Remarks

Fatigue continues to be used without widely agreed upon definitions or gold standard measures. Consequently, our knowledge of interventions including pharmacologic, lifestyle (e.g., physical activity), and others (e.g., transcranial magnetic stimulation) that may be most appropriate to manage fatigue, remains limited. Interventions that do exist remain tied to an ill-defined symptom and do not typically yield improvements (Fernandez-Carbonell, Charvet, & Krupp, 2021; Kluger, Krupp, & Enoka, 2013; Storm Van's Gravesande et al., 2019).

Taken together, we must consider the generalizabilty of our research findings and integrate more ecologically valid approaches to the study of fatigue. This may aid in our comprehension of how fatigue impacts thinking and functional skills such as those required for independence and activities of daily living, academic and workplace performance, decision making and adapting to changes in the environment, learning & memory, and safety.

In closing, this dissertation contributes to the small fatigue literature in POMS. The first study highlighted the ongoing issue of methodological heterogeneity across the limited existing research. Given the substantial impact of fatigue on the quality of life in patients with POMS, further research is needed to understand fatigue determinants and valid objective measurement methods. It is believed to be the first study to have examined IIV as a behavioural correlate of subjective fatigue in POMS. Our findings from both included studies align with the literature – the prior systematic review by Carroll and colleagues (2016), and studies of variability in AOMS.

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Appendix A: Supplemental Documents

Supplemental Document 1. Search strategy by database

Medline	Embase	PsycInfo	Web of Science	CINAHL
1. P?ediatric.mp OR exp Pediatrics/	1. P?ediatric. mp OR exp Pediatrics/	1. P?ediatric.mp OR exp Pediatrics/	((P$ediatric OR Child* OR Adolescen* OR Juvenile OR Young Person OR Young People OR Early-onset) AND (Multiple sclerosis OR MS OR Disseminated Sclerosis OR Encephalomyelitis Disseminata OR Demyelinating Disease) AND (Fatigue OR Weak OR Weakness OR Tired OR Tiredness OR Lethargy OR Lethargic) AND (Cognit*))	1. P#ediatric
2. Child*.mp OR Child/	2. Adolescen*.mp	2. Child*.mp		2. MH Pediatrics+
3. Adolescen*.mp OR exp Adolescent/	3. Exp Adolescence/	3. Adolescen*mp		3. Adolescen* OR MH Adolescence+
4. Juvenile.mp	4. Child*.mp	4. Juvenile.mp		4. Child*
5. Early-onset.mp	5. Exp Child/	5. Early-onset.mp		5. MH Child+
6. Young person.mp	6. Juvenile.mp	6. Young person.mp		6. Juvenile
7. Young people.mp	7. Early-onset.mp	7. Young people.mp		7. Young Person
8. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7	8. Young person.mp	8. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7		8. Young People

9. Multiple Sclerosis.mp OR exp Multiple Sclerosis/	9. Young people.mp	9. Multiple Sclerosis.mp OR exp Multiple Sclerosis/		9. Early-onset
10. MS.mp	10. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9	10. MS.mp		10. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9
11. Disseminated sclerosis.mp	11. Multiple Sclerosis.mp OR exp Multiple sclerosis/	11. Disseminated Sclerosis.mp		11. Multiple Sclerosis OR MH Multiple Sclerosis
12. Encephalomyelitis disseminata.mp	12. MS.mp	12. Encephalomyelitis Disseminata.mp		12. MS
13. Demyelinating disease.mp	13. Disseminated sclerosis.mp	13. Demyelinating disease.mp		13. Disseminated Sclerosis
14. 9 OR 10 OR 11 OR 12 OR 13	14. Encephalomyelitis disseminata.mp	14. 9 OR 10 OR 11 OR 12 OR 13		14. Encephalomyelitis Disseminata
15. 8 AND 14	15. Demyelinating disease.mp	15. 8 AND 14		15. Demyelinating disease
16. Fatigue.mp OR exp Fatigue/	16. 11 OR 12 OR 13 OR 14 OR 15	16. Fatigue.mp OR exp Fatigue/		16. 11 OR 12 OR 13 OR 14 OR 15
17. Mental Fatigue.mp OR exp Mental Fatigue/	17. 10 AND 16	17. Weak*.mp OR exp Weak/		17. 10 AND 16
18. Weak*.mp OR exp Weak/	18. Fatigue.mp OR exp Fatigue/	18. Tired*.mp OR exp Tired		18. MH Fatigue+ OR Fatigue
19. Tired*.mp OR exp Tired	19. Weak*.mp OR exp Weak/	19. Letharg*.mp OR exp Lethargic		19. Weak*
20. Letharg*.mp OR exp Lethargy	20. Tired*.mp OR exp Tired	20. 16 OR 17 OR 18 OR 19		20. Tired*
21. 16 OR 17 OR 18 OR 19 OR 20	21. Letharg*.mp	21. 15 AND 20		21. Letharg*

	OR exp Lethargic			
22. 15 AND 21	22. 18 OR 19 OR 20 OR 21	22. Cognitive Assessment.mp		22. 18 OR 19 OR 20 OR 21
23. Neuropsychological Tests.mp OR exp Neuropsychological Tests	23. 17 AND 22	23. Cognitive Processes.mp		23. 17 AND 22
24. Cognition Disorders.mp OR exp Cognition Disorders	24. Cognition.mp OR exp Cognition/	24. Cognitive Ability.mp		24. MH "Cognition Disorders") OR "cognitive"
25. Cognitive Dysfunction.mp OR exp Cognitive Dysfunction	25. 23 AND 24	25. Cognitive Processing Speed.mp		25. 23 AND 24
26. Cogniti*.mp OR exp Cognition/		26. 22 OR 23 OR 24 OR 25		
27. 23 OR 24 OR 25 OR 26		27. 21 AND 26		
28. 22 AND 27				

Supplemental Document 2. JBI critical appraisal checklist for analytical cross-sectional studies

JBI CRITICAL APPRAISAL CHECKLIST FOR ANALYTICAL CROSS SECTIONAL STUDIES

Reviewer____________________________________Date______________________________

Author____________________________________Year_________ Record Number_________

	Yes	No	Unclear	Not applicable
1. Were the criteria for inclusion in the sample clearly defined?	☐	☐	☐	☐
2. Were the study subjects and the setting described in detail?	☐	☐	☐	☐
3. Was the exposure measured in a valid and reliable way?	☐	☐	☐	☐
4. Were objective, standard criteria used for measurement of the condition?	☐	☐	☐	☐
5. Were confounding factors identified?	☐	☐	☐	☐
6. Were strategies to deal with confounding factors stated?	☐	☐	☐	☐
7. Were the outcomes measured in a valid and reliable way?	☐	☐	☐	☐
8. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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EXPLANATION OF ANALYTICAL CROSS SECTIONAL STUDIES CRITICAL APPRAISAL

How to cite: Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Qureshi R, Mattis P, Lisy K, Mu P-F. Chapter 7: Systematic reviews of etiology and risk . In: Aromataris E, Munn Z (Editors). *JBI Manual for Evidence Synthesis.* JBI, 2020. Available from https://synthesismanual.jbi.global

Analytical cross sectional studies Critical Appraisal Tool

Answers: Yes, No, Unclear or Not/Applicable

1. Were the criteria for inclusion in the sample clearly defined?

The authors should provide clear inclusion and exclusion criteria that they developed prior to recruitment of the study participants. The inclusion/exclusion criteria should be specified (e.g., risk, stage of disease progression) with sufficient detail and all the necessary information critical to the study.

2. Were the study subjects and the setting described in detail?

The study sample should be described in sufficient detail so that other researchers can determine if it is comparable to the population of interest to them. The authors should provide a clear description of the population from which the study participants were selected or recruited, including demographics, location, and time period.

3. Was the exposure measured in a valid and reliable way?

The study should clearly describe the method of measurement of exposure. Assessing validity requires that a 'gold standard' is available to which the measure can be compared. The validity of exposure measurement usually relates to whether a current measure is appropriate or whether a measure of past exposure is needed.

Reliability refers to the processes included in an epidemiological study to check repeatability of measurements of the exposures. These usually include intra-observer reliability and inter-observer reliability.

4. Were objective, standard criteria used for measurement of the condition?

It is useful to determine if patients were included in the study based on either a specified diagnosis or definition. This is more likely to decrease the risk of bias. Characteristics are another useful approach to matching groups, and studies that did not use specified diagnostic methods or definitions should provide evidence on matching by key characteristics

5. Were confounding factors identified?

Confounding has occurred where the estimated intervention exposure effect is biased by the presence of some difference between the comparison groups (apart from the exposure investigated/of interest). Typical confounders include baseline characteristics, prognostic factors, or concomitant exposures (e.g. smoking). A confounder is a difference between the comparison groups and it influences the direction of the study results. A high quality study at the level of cohort design will identify the potential confounders and measure them (where possible). This is difficult for studies where behavioral, attitudinal or lifestyle factors may impact on the results.

6. Were strategies to deal with confounding factors stated?

Strategies to deal with effects of confounding factors may be dealt within the study design or in data analysis. By matching or stratifying sampling of participants, effects of confounding factors can be adjusted for. When dealing with adjustment in data analysis, assess the statistics used in the study. Most will be some form of multivariate regression analysis to account for the confounding factors measured.

7. Were the outcomes measured in a valid and reliable way?

Read the methods section of the paper. If for e.g. lung cancer is assessed based on existing definitions or diagnostic criteria, then the answer to this question is likely to be yes. If lung cancer is assessed using observer reported, or self-reported scales, the risk of over- or under-reporting is increased, and objectivity is compromised. Importantly, determine if the measurement tools used were validated instruments as this has a significant impact on outcome assessment validity.

Having established the objectivity of the outcome measurement (e.g. lung cancer) instrument, it's important to establish how the measurement was conducted. Were those involved in collecting data trained or educated in the use of the instrument/s? (e.g. radiographers). If there was more than one data collector, were they similar in terms of level of education, clinical or research experience, or level of responsibility in the piece of research being appraised?

8. Was appropriate statistical analysis used?

As with any consideration of statistical analysis, consideration should be given to whether there was a more appropriate alternate statistical method that could have been used. The methods section should be detailed enough for reviewers to identify which analytical techniques were used (in particular, regression or stratification) and how specific confounders were measured. For studies utilizing regression analysis, it is useful to identify if the study identified which variables were included and how they related to the outcome. If stratification was the analytical approach used, were the strata of analysis defined by the specified variables? Additionally, it is also important to assess the appropriateness of the analytical strategy in terms of the assumptions associated with the approach as differing methods of analysis are based on differing assumptions about the data and how it will respond.

Supplemental Document 3. Systematic review full data extraction table (by year)

Title	Author(s), Year	Country	Study Design	Sample (n), M_{age} (SD; range)	Clinical l, psychological (P), social (S), and (O) factors measured	Main Results	Key Limitation(s)
Cognitive functioning in children and adolescents with multiple sclerosis	MacAllister et al., 2005	USA	Cross-Sectional	**MS** (n=37), 14.9 (2.2; 8-17)	**C:** EDSS, age, sex, age at symptom onset, disease duration, number of relapses, MS type, DMTs **P:** brief neuropsychological battery (attention, rapid visual scanning and motor speed, language, verbal fluency and naming ability, receptive language, memory, graphomotor construction), psychological function (Schedule for Affective Disorders and Schizophrenia for School Aged Children), fatigue (dichotomous yes/no self-report) **O:** academic assistance in school	**Proportion of POMS with Fatigue:** 48.6% **Association with Cognition:** self-reported fatigue was not correlated with cognition	1) lack of age- and demographic-matched controls, 2) not all patients received a psychiatric evaluation
Cognitive and psychosocial features of childhood and juvenile MS	Amato et al., 2008	Italy	Cohort*	**MS** (n=63), 15.3 (2.5; 8.8-17.9) **HC** (n=57), 14.8 (3.5; 8.1-17.9)	**C:** EDSS, age, sex, age at onset, disease duration, number of relapses, DMTs **P:** extensive neuropsychological battery (IQ, verbal learning, visuospatial learning, sustained attention and concentration (including SDMT), abstract reasoning, expressive language, receptive language), self-assessed depressive symptoms (CDI), fatigue (FSS) **S:** school activities, hobbies, sports, family and social relationships in the previous year **O:** education	**Proportion of POMS with Fatigue:** 14.3%, fatigue comparable in the group with and without cognitive impairment **Association with Cognition:** not found **Other Associations:** an IQ score in the inferior range correlated with CI, low IQ was significantly associated with younger age at onset	1) Fatigue Severity Scale cut-off for adults may not be fully adequate to capture symptoms in a pediatric population and some items may require adaptation/modification, 2) proposed underestimate of depression due to low sensitivity in assessment
Cognitive and psychosocial features in childhood and juvenile MS: two-year follow-up	Amato et al., 2010	Italy	Cohort*	**MS** (n=56), MS group 1: 12.5 (1.3; 10.9-14.4), MS group 2: 17.9 (1.8; 15-20.6) **HC** (n=50), HC group 1: 11.2 (1.8; 8.9-14.6), HC group 2 18.6 (2.4; 15.1-20.8)	**C:** EDSS, age, sex, age at onset, disease duration, number of relapses, DMTs P: extensive neuropsychological battery (verbal learning, visuospatial learning, complex attention (including SDMT), planning, expressive language), self-assessed depressive symptoms (CDI and Kiddie-SADS), fatigue (FSS) **S:** school activities, hobbies, sports, family and social relationships in the	**Proportion of POMS with Fatigue:** 21% **Association with Cognition:** not found **Other Associations:** older age was the only significant predictor of cognitive deterioration	1) Fatigue Severity Scale cutoff for adults may not be fully adequate to capture symptoms in a pediatric population, proposed as a barrier to documenting an association with cognition

					previous year **O:** education		
Fatigue and its relationships with cognitive functioning and depression in paediatric multiple sclerosis	Goretti et al., 2012	Italy	Cross-Sectional*	**MS** (n=57), 16.6 (2.5; 11-20) **HC** (n=70), 16 (3; 11-20)	**C:** EDSS, age, disease duration, number of relapses in the last year, DMTs **P:** extensive neuropsychological battery (verbal learning, visuospatial learning, complex attention (including SDMT), planning, expressive language), self-assessed depressive symptoms (CDI and Kiddie-SADS), fatigue (PedsQL-MFS) **O:** education	**Proportion of POMS with Fatigue:** 9–14% according to self-reports, and 23–39% according to parent reports **Association with Cognition:** fatigue and psychiatric disorders were not related to the number of tests failed, overall cognitive impairment, or worsening cognitive performance at follow-up, though higher levels of self- and parent-reported cognitive fatigue associated with four specific tests (i.e., Tower of London Test, Selective Reminding Test – Long Term Storage, TMT B, and Token Test).	1) some patients older than 18 years at the time of data collection, 2) years of education and social measures not matched between parents of MS patients and HC parents, 3) HCs did not undergo a formal psychiatric interview with the K-SADS-PL, though depression was screened with the CDI
Neuropsychological features in childhood and juvenile multiple sclerosis: Five-year follow-up	Amato et al., 2014	Italy	Cohort*	**MS** (n=48), MS group 1: 14.5 (0.9; 10-16), MS group 2: 20.5 (1.9; >16) **HC** (n=46), HC group 1: 14.6 (1.5; 10-16), HC group 2: 21.6 (2.3; >16)	**C:** EDSS, age, sex, age at onset, disease duration, number of relapses, DMTs **P:** extensive neuropsychological battery (verbal learning, visuospatial learning, complex attention (including SDMT), planning, expressive language), self-assessed depressive symptoms (CDI), fatigue (FSS) **S:** school activities, hobbies, sports, family and social relationships in the previous year **O:** education	**Proportion of POMS with Fatigue:** 20% of patients (22% at year 2) **Association with Cognition:** not found **Other Associations:** CI and poor functional outcomes were correlated, fatigue and depression were related	1) sample may not be representative of the general POMS population, 2) results suggested that male sex, younger age and age at disease onset, and lower educational level were related to cognitive impairment; however, these variables were not retained in the multivariate analysis, thus predictors of individual cognitive outcome were not considered, 3) monitoring instruments may not have been sensitive enough to detect associations of clinical and psychological factors with cognition

Neuropsychological functioning in pediatric multiple sclerosis: A longitudinal investigation of cognitive performance and the contribution of primary clinical factors	Canas, 2014	USA	Cohort	**MS** (n=20), 14.8 (2.1, 9-18)	**C:** ambulation index, age, sex, age at onset, disease duration, relapse rate **P:** extensive neuropsychological battery (IQ, verbal learning, executive functioning, visual-motor functioning and processing speed (including SDMT), behaviour and emotion (BASC-2), fatigue (PedsQL-MFS)	**Proportion of POMS with Fatigue:** proportion not reported, overall self-reported fatigue fell in the mildly elevated range using range defined by MacAllister et al., (2009) **Association with Cognition:** TMT A emerged as most vulnerable to change as a function of fatigue **Other Associations:** relationship between greater depression and decreased performance found for several tasks	1) modest sample size may have contributed to low statistical power, particularly for regression analyses, 2) study is limited by demographic characteristics of sample, 3) study design may have caused statistical regression towards mean and practice effects, 4) study lacked a control group for comparison, 5) some neuropsychological battery tests (e.g., TMT, GPT) may be based on poor, incomplete or dated standardization methods, 6) no consideration of resiliency, treatment effects and cognitive reserve on attention, memory etc., 7) authors did not consider change at the individual level
Fatigue, emotional functioning, and executive dysfunction in pediatric multiple sclerosis	Holland et al., 2014	USA	Retrospective	**MS** (n=26), 15.2 (2.4; 7-18)	**C:** ambulation, age, sex, age at onset, disease duration, DMTs **P:** brief neuropsychological battery (letter fluency, working memory, sustained attention and mental manipulation, working memory and cognitive flexibility), emotional functioning (PedsQL, BRIEF, BASC-2), fatigue (PedsQL-MFS) **O:** ethnicity	**Proportion of POMS with Fatigue:** proportion not reported, mean parent-reported general and total fatigue were severe, while cognitive and sleep fatigue were mildly impaired, parents more frequently reported significant concerns regarding fatigue than the patients, smallest percentage of significant concerns in the domain of sleep/rest fatigue per parent- and self-report **Association with Cognition:** parent-reported general fatigue was moderately correlated with performance on TMT B and self-reported general fatigue demonstrated a moderate correlation with performance on TMT A and B	1) small sample size, 2) lack of comparison/control group, 3) no data on socioeconomic status, nor history of psychological and cognitive problems, 4) disease duration was relatively short

Psychological and psychosocial correlates of executive functioning in pediatric multiple sclerosis	Nunan-Saah, 2015	USA	Cross-Sectional**	**MS** (n=79), 14.5 (2.9; 6.5-18)	**C:** EDSS, age, sex, age at onset, disease duration **P:** comprehensive network battery (Pediatric Multiple Sclerosis Centers of Excellence battery, Brief Visuospatial Memory Test-Revised, Delis Kaplan Executive Function System Verbal Fluency Test), behaviour (BRIEF, BASC-2), quality of life (PedsQL, PedsQL-FIM), fatigue (PedsQL-MFS) **O:** parental education, race, ethnicity (Hispanic or Non-Hispanic)	**Proportion of POMS with Fatigue:** <u>not reported</u> **Association with Cognition:** performance-based measures of executive functioning did not significantly predict measures of psychosocial functioning including fatigue, whereas self-report measures of executive functioning were predictive of all measures of self-and parent-reported psychosocial functioning including fatigue **Other Associations:** depression and anxiety predicted aspects of psychosocial functioning including fatigue	1) relatively short disease duration, 2) test scores were restricted in range because patients showed less severe cognitive, psychosocial, and psychological functioning than what is expected in more severe outpatient or inpatient populations and this may have impacted the correlations, 3) sample sizes for each neuropsychological measure and self-report questionnaire were smaller resulting in lower power, 4) possible variations in battery content, order, and length, 5) no control group
Behavioral symptoms in pediatric multiple sclerosis: Relation to fatigue and cognitive impairment	Charvet et al., 2016	USA	Cross-Sectional	**MS** (n=108) **CIS** (n=32) Full sample: 14.9 (2.6; 5.9-18)	**C:** EDSS, age, sex, age at disease onset, disease duration **P:** neuropsychological evaluation (IQ, reading and language, attention, working memory, and speeded processing, executive functioning, verbal episodic learning and recall, visuospatial functioning, fine motor speed and coordination), emotional and behavioural symptoms (BASC-2), fatigue (FSS) **O:** race, ethnicity	**Proportion of POMS with Fatigue:** proportion not reported, mild to moderate overall **Association with Cognition:** cognitive functioning (composite z score) and fatigue were not significantly related	1) no control group for comparison, 2) only a subset of the sample (n=66) completed the fatigue measure
The computer-based Symbol Digit Modalities Test: establishing age-expected performance in healthy controls and evaluation of pediatric MS patients	Bigi et al., 2017	Canada	Cross-Sectional	**MS** (n=27), Median (IQR) 15.7 **HC** (n=478)	**C:** EDSS, age, sex, age at first attack, disease duration, medication, giftedness, medical history **P:** information processing speed (c-SDMT), fatigue (Reported level of tiredness completing the test ("not at all", "a little bit", "very tired") **O:** education	**Proportion of POMS with Fatigue:** proportion not reported, tiredness did not differ between MS and HC; **Association with Cognition:** demographic and clinical characteristics were not associated with median IPS	1) subjective tiredness about the task may not be an accurate measure of cognitive fatigue, 2) more validation of the c-SDMT is needed

Executive functioning in pediatric multiple sclerosis: Considering the impact of emotional and psychosocial factors	Nunan-Saah et al., 2017	USA	Retrospective**	**MS** (n=65), 14.6 (3; 6.5-18)	**C:** EDSS, age, sex, age at onset, disease duration **P:** comprehensive neuropsychological battery (IQ, executive functioning, verbal fluency), self-and parent-reported behaviour (BRIEF, BASC-2), quality of life (PedsQL), fatigue (PedsQL-MFS) **O:** parental education level	**Proportion of POMS with Fatigue:** proportion not reported **Association with Fatigue:** performance-based measures of executive functioning were not significantly correlated with any psychosocial variables, the BRIEF Self- and Parent-Report accounted for an additional 51% of the variance in self-reported fatigue after controlling for significant patient and disease factors and in a separate regression the BRIEF Parent- and Self-Report accounted for an additional 41% of the variance in parent-reported fatigue	1) average disease duration for participants was relatively short, 2) sample sizes for each neuropsychological measure and self-report questionnaire were smaller resulting in lower power, 3) did not ascertain sociodemographic and clinical variables that may influence neuropsychological performance in children (due to the retrospective nature of the study)
Adolescent and parent factors related to fatigue in paediatric multiple sclerosis and chronic fatigue syndrome: A comparative study	Carroll et al., 2019	UK	Observational Cross-Sectional Comparative	**MS** (n=30; 15 fatigued and 15 non-fatigued), 15.9 (9.3-19) **CFS** (n=30), 15.7 (12.2-18) **HC** (n=30), 15 (8.5-18.5)	**C:** age, gender, age at onset, disease duration, relapse in past year, DMTs **P:** global cognitive functioning (IQ), cognitive and behavioural responses to symptoms, psychological difficulties, parental distress, fatigue "case-ness" (Chalder Fatigue Questionnaire), fatigue severity (PedsQL-MFS) **S:** school attendance rate, functional impairment **O:** nationality, sleep behaviour	**Proportion of POMS with Fatigue:** 50% **Association with Cognition:** not found **Other Associations:** fatigued MS patients showed greater fatigue severity, functional impairment, and responses to symptoms vs. non-fatigued MS patients and HCs, comparable between MS and CFS	1) low power due to small sample size, particularly where patients were parceled into fatigued and non-fatigued subgroups, 2) missing neurocognitive data may have limited the conclusions that could be drawn from between-group comparisons, 3) sample may not be representative as patients opted into the study and some patients from specialist services did not provide informed consent to participate

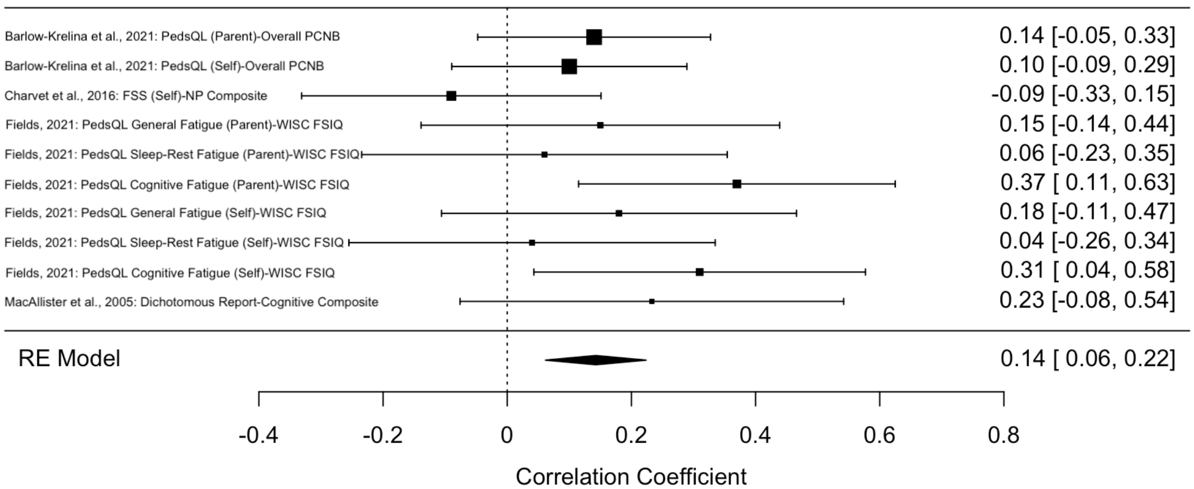
Cognitive reserve is a determinant of social and occupational attainment in patients with pediatric and adult onset multiple sclerosis	Portaccio et al., 2020	Italy	Cross-Sectional	**POMS** (n=111) **AOMS** (n=115)	**C:** EDSS, age, sex, age at onset, disease duration, DMTs **P:** neuropsychological battery (Brief Repeatable Battery of Neuropsychological Tests, Stroop Test including SDMT), depression (Montgomery-Åsberg Depression Rating Scale), fatigue (FSS) **S:** work and social adjustment (Work and Social Adjustment Scale) **O:** education, cognitive reserve (total education + National Adult Reading Test-Italian Version), socio-economic status (BSMSS)	**Proportion of POMS with Fatigue:** proportion not reported **Association with Cognition:** not found **Other Associations:** factors associated with cognitive impairment included older age, higher EDSS, and lower IQ	1) relatively small sample size, 2) cross-sectional design, 3) difference in mean age of POMS vs. AOMS patients may have underestimated the burden of cognitive impairment in POMS in comparison to AOMS, unless the longer disease duration in POMS patients may have exposed them to the negative disease-related effects on cognitive functions for a longer period of time
Examining cognitive speed and accuracy dysfunction in youth and young adults with pediatric-onset multiple sclerosis using a computerized neurocognitive battery	Barlow-Krelina et al., 2021	Canada/ USA	Cross-Sectional	**MS** (n=65), 18.3 (4; 8-27) **HC** (n=76), 18.1 (4.6; 8-29)	**C:** EDSS, age, sex, age at MS onset, disease duration from the first attack, DMTs **P:** computerized neurocognitive battery (Penn Computerized Neurocognitive Battery), information processing speed (SDMT), emotional distress (PIED (age < 16) or HADS (age > 16)), fatigue (PedsQL-MFS) **O:** participant and parent education, nationality, SES	**Proportion of POMS with Fatigue:** proportion not reported **Association with Cognition:** not found **Other Associations:** only longer disease duration was associated with poorer accuracy on the Line Orientation and Verbal Memory tests after adjusting for covariates	1) potentially the approach to z-score creation (age-bands), 2) the pediatric version of the PCNB was not age appropriate for some of the older patients (i.e., ceiling effects observed, therefore possibly too simple)
Fatigue and cognitive functioning in pediatric onset multiple sclerosis	Fields, 2021	USA	Retrospective	**MS** (n=49), 14.1 (2.8)	**C:** age, sex, handedness **P:** comprehensive neuropsychological battery (National MS Society Consensus Neuropsychological Battery for Pediatric MS (including SDMT)), emotional and behaviour problems (self- and parent-reported BRIEF, BASC-2), quality of life (PedsQL), fatigue (PedsQL-MFS) **O:** parental education, race/ethnicity	**Proportion of POMS with Fatigue:** proportion not reported, fatigue did not differ between patients with cognitive impairment and those without **Association with Cognition:** moderate to strong relationships between subjective cognitive fatigue and higher order verbal executive functioning and response time on a sustained attention task	1) small sample size may have impacted statistical power and generalizability of findings, 2) wide age range may have contributed to increased heterogeneity within the sample, 3) study did not include a HC group, 4) limited focus on the impact of POMS disease variables on the relationship between neuropsychological performance and rates of subjective fatigue, 5) subjective measures of fatigue may capture other phenomena such as symptoms of

							depression, 6) the PedsQL-MFS assesses fatigue over the past month vs. in the same moment the cognitive data are collected

Abbreviations. BASC-2: Behaviour Assessment System for Children: Second Edition; BRIEF: Behaviour Rating Inventory of Executive Function; BSMSS: Barratt Simplified Measure of Social Status; CDI: Children's Depression Inventory; CI: cognitive impairment; CFS: Chronic Fatigue Syndrome; CIS: Clinically Isolated Syndrome; DMTs: Disease Modifying Therapies; EDSS: Expanded Disability Status Scale; FSS: Fatigue Severity Scale; HADS: Hospital Anxiety and Depression Scale; HCs: healthy controls; IPS: information processing speed; IQR: Interquartile range; MS: multiple sclerosis; PCNB: Penn Computerized Neurocognitive Battery; PedsQL-FIM: Family Impact Module; PedsQL-MFS: Pediatric Quality of Life Inventory Multidimensional Fatigue Scale; POMS: pediatric-onset multiple sclerosis PIED: Pediatric Index of Emotional Distress; SDMT: Symbol Digit Modalities Test; SES: socioeconomic status; TMT: Trail Making Test

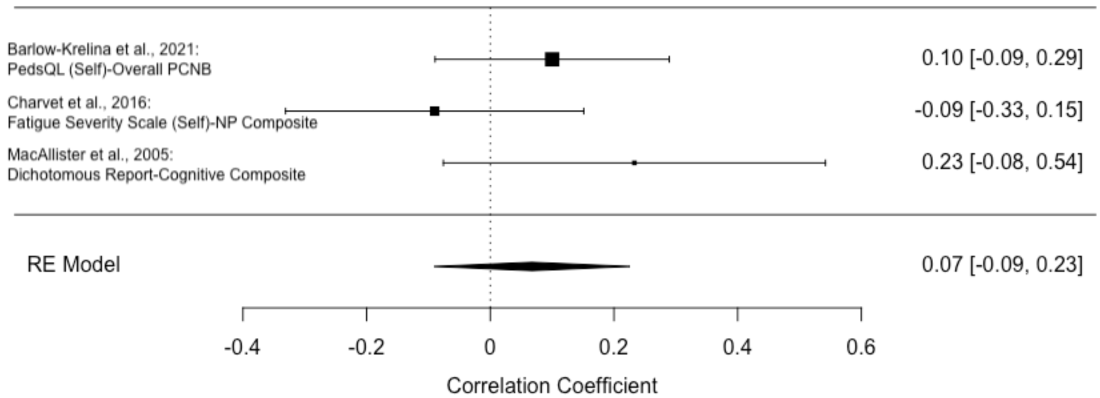
Note. [*]from shared Italian patient cohort; [**]from same archival dataset but may include different participants

Supplemental Document 4. Meta-analytic models and interpretation



Supplemental Figure 4a. *Meta-analysis of the studies reporting a correlation coefficient of the relationship between fatigue and cognition*

The results of the meta-analysis shown in Supplemental Figure 4a revealed a small, statistically significant positive effect of fatigue on the cognitive outcome (B=0.14, SE=0.04, 95% CI [0.06, 0.22], p<.001). A limitation of the model shown above is that we included several outcomes from the same study which conflicts with the purpose of a meta-analysis (i.e., to group correlated subscales/outcomes from different studies). To address this, we conducted a sensitivity analysis (Supplemental Figure 4b) that only included studies that reported a PedsQL-MFS (Varni et al., 2002) total score. We also elected to look only at self-reports (not parent-reports) of total fatigue. This second model (Supplemental Figure 4b) is limited by the inclusion of only three studies that report different types of correlation coefficients.



Supplemental Figure 4b. *Meta-analysis of the studies reporting a correlation coefficient of the relationship between total self-reported fatigue and cognition*

Overall, this meta-analysis suggests that there is no statistically significant effect of fatigue on the cognitive composite score (B=0.07, SE=0.08, p=.40), but this is a very limited view of the literature. Like before, the test for heterogeneity was not statistically significant (τ^2=.00, SE=0.02, Q(df=2)=2.85, p=.24). While the overall confidence interval for the estimate was smaller (ranging from -0.09 to 0.23) than any one study included, the analysis was underpowered. As such, the 2016 study by Charvet and colleagues had enough weight in the analysis to make the overall result cross zero.

Appendix B: Supplemental Tables

Supplemental Table A. List of tests in standard battery (in order of administration)

Subtest	Domain	Neurobehavioural function	Brief description
Motor Praxis Test	Sensorimotor	Motor planning and coordination	Quickly manipulate a computer mouse to click on a target that moves and changes size
Measured Emotion Differentiation Test	Social Cognition	Emotion differentiation	Identify which of two faces is showing an emotion to a greater degree
Penn Verbal Reasoning Test	Complex Cognition	Verbal reasoning	Select from a list the word that best completes the verbal analogy
Face Memory Test	Episodic Memory	Face recognition memory	Identify which faces have been seen previously
Emotion Recognition Test	Social Cognition	Emotion identification	Identify the emotion shown on a given face from a list of emotions
Letter N-Back	Executive Function	Working memory, shifting	One letter shown on screen at a time; press according to three rules, across three different conditions: (1) press for X, (2) press when the current letter is the same as the previous letter, (3) press when the current letter is the same as the letter that came before the previous letter - respond when the appropriate letter is displayed amongst a series of letters

Word Memory Test	Episodic Memory	Verbal recognition memory	Identify which words have been seen previously
Age Differentiation Test	Social Cognition	Age differentiation, visual discrimination	Identify which of two faces is older
Variable Penn Line Orientation Test	Complex Cognition	Spatial ability, visual discrimination	Rotate a line until it is parallel to a fixed line of a different length and orientation, using as few clicks as possible
Visual Object Learning Test	Episodic Memory	Spatial recognition memory	Identify which figures have been seen previously
Penn Matrix Analysis Test	Complex Cognition	Nonverbal reasoning	Choose the geometric piece that best completes the pattern
Penn Continuous Performance Test	**Executive Function**	Sustained attention	Press for a letter/number; do not press for distractor items
Penn Conditional Exclusion Test	Executive Function/Complex Cognition	Cognitive flexibility, rule learning, working memory	Identify which object of four does not belong based on one of three sorting principles; sorting principles switch after 10 consecutive objects selected correctly
Go-No-Go Test	Executive Function	Inhibitory control, sustained attention	Press for target letter in upper half of screen; do not press for nontarget letter or for letters in lower half of screen
Computerized Finger-Tapping Task	**Sensorimotor**	Fine motor speed	Tap the spacebar using only the index finger as many times as possible within 10,000ms

Note. Subtests in bold are the primary outcomes used in the current study.

Supplemental Table B. T1-weighted MPRAGE sequences per the standardized research protocol

Sequence List
T1-weighted MPRAGE (TR 1810 ms, TE 3.51 ms, TI 1100 ms, flip angle 9˚, 160 slices, voxel size 0.9 x 0.9 x 1 mm^3)
3D FLASH with and without a magnetization transfer pulse to compute magnetization transfer ratio (MTR; TR 33 ms, TE 3.86 ms, flip angle 10˚, 192 slices, voxel size 1 x 1 x 1 mm^3, GRAPPA factor 2)
Dual-angle B1 mapping pair (EPI- SE, TR 4000 ms, TE 18 ms, voxel size 2 x 2 x 5 mm^3, flip angles 60˚and 120˚)
2D TSE proton density (PD)-weighted (TR 2200 ms, TE 10 ms, 60 slices, ETL 4, voxel size 1 x 1 x 3 mm^3)
2D 26 TSE T2-weighted (TR 4500 ms, TE 84 ms, 60 slices, ETL 11, voxel size 1 x 1 x 3 mm^3)
3D FLAIR (TR 5000 ms, TE 388 ms, TI 1800 ms, ETL 155, 208 slices, voxel size 1 x 1 x 1 mm^3), DTI (TR 10300 ms, TE 94 ms, 30 diffusion-encoding directions, 50 slices, voxel size 2 x 2 x 2 mm^3, GRAPPA factor 2)
T1-weighted pre/post gadolinium (3D FLASH TR 30 ms, TE 6.15 ms, flip angle 27˚, 60 slices, voxel size 1 x 1 x 3 mm^3)

Supplemental Tables C. Sensitivity analyses with correct responses only

a) Between-group differences (POMS-HC) in IIV outcomes from the multiple linear regression presented as estimated marginal means (robust modeling) – correct responses

Outcome	POMS (n=34) M(SE)	HC (n=63) M(SE)	B(SE)	*p*	95% Confidence Interval for effect estimate Lower	Upper	Multiple R^2
IIV (ISD; ms)[a]	106.70 (4.17)	93.40 (3.05)	13.33 (5.26)	**.01**	3.19	23.48	.17
IIV (COV; %)[a]	18.7 (0.63)	16.3 (0.46)	2.43 (0.76)	**.002**	0.91	3.95	.15

Abbreviations: COV: coefficient of variation; CPT: Continuous Performance Test; HC: healthy control; IIV: intra-individual variability; ISD: individual standard deviation; POMS: pediatric-onset multiple sclerosis

[a]controlling for age, sex, and parental education

Note. Sample sizes are reduced due to missing parental education data for one patient and seven HCs.

b) Correlations (two-tailed) between subjective fatigue and IIV - correct responses

IIV Outcome	Group	n	**Correlations** **Parent-rated** Total Fatigue	General Fatigue	Sleep-Rest Fatigue	Cognitive Fatigue
ISD	All	70	r_s=.01, *p*=.91	r_s=-.02, *p*=.88	r_s=.16, *p*=.20	r_s=-.15, *p*=.22
	POMS	28	r_s=.25, *p*=.21	r_s=.13, *p*=.51	r_s=.26, *p*=.18	r_s=.06, *p*=.77
	HC	42	r_s=-.07, *p*=.68	r_s=-.02, *p*=.89	r_s=.21, *p*=.19	r_s=-.22, *p*=.15
COV	All	70	r_s=.01, *p*=.96	r_s=.00, *p*=.97	r_s=.14, *p*=.26	r_s=-.13, *p*=.29
	POMS	28	r_s=.23, *p*=.24	r_s=.19, *p*=.34	r_s=.27, *p*=.18	r_s=.02, *p*=.91
	HC	42	r_s=-.07, *p*=.66	r_s=-.01, *p*=.95	r_s=.16, *p*=.31	r_s=-.19, *p*=.22
			Self-rated			
ISD	All	91	r_s=.21, *p*=.05	r_s=.22, *p*=.04	r_s=.23, *p*=.03	r_s=.11, *p*=.28
	POMS	33	**r_s=.48, *p*<.01**	r_s=.43, *p*=.01	**r_s=.57, *p*<.001**	r_s=.31, *p*=.08
	HC	58	r_s=.05, *p*=.70	r_s=.10, *p*=.42	r_s=.00, *p*=1.00	r_s=.01, *p*=.95
COV						
	All	91	r_s=.15, *p*=.16	r_s=.16, *p*=.14	r_s=.17, *p*=.10	r_s=.07, *p*=.52
	POMS	33	r_s=.36, *p*=.04	r_s=.35, *p*=.05	r_s=.42, *p*=.02	r_s=.21, *p*=.24

HC	58	r_s=.01, *p*=.96	r_s=.05, *p*=.71	r_s=-.01, *p*=.95	r_s=-.04, *p*=.77

Abbreviations: COV: coefficient of variation; CPT: Continuous Performance Test; HC: healthy control; ISD: individual standard deviation; POMS: pediatric-onset multiple sclerosis

c) Whole brain white matter FA as a correlate of CPT fatigability in POMS patients and HCs (robust modelling) – correct responses

DTI Metric	B(SE)	*p*	95% Confidence Interval for effect estimate: Lower	Upper	Multiple R^2
Whole Brain FA (0 – 1)					
IIV: ISD (POMS)	-5.24 (8.70)	.55	-18.54	8.07	.20
IIV: COV (%) (POMS)	-0.57 (1.21)	.64	-2.51	1.37	.20
IIV: ISD (HC)	-0.08 (7.10)	.99	-10.29	10.13	.18
IIV: COV (%) (HC)	0.15 (1.17)	.90	-1.43	1.73	.10

Abbreviations: COV: coefficient of variation; CPT: Continuous Performance Test; ISD: individual standard deviation; POMS: pediatric-onset multiple sclerosis
Note. Models were adjusted for age, sex, and parental education. Beta values were adjusted (i.e., divided by 100) to represent a 0.01 increase in FA. POMS (n=30); HC (n=51)

Supplemental Table D. Group differences (POMS-HC) in IIV outcomes from the multiple linear regression presented as estimated marginal means (robust modelling) accounting for omission responses

Outcome	**POMS (n=34)** M(SE)	**HC (n=63)** M(SE)	B(SE)	*p*	**95% Confidence Interval for effect estimate** Lower	Upper	Multiple R^2
IIV (ISD; ms)[a]	179.00 (5.86)	156.00 (4.29)	23.67 (7.00)	**.001**	9.43	37.92	.25
IIV (COV; %)[a]	30.70 (0.75)	27.00 (0.55)	3.73 (0.89)	**<.001**	1.90	5.55	.23
Mean RT (ms)[a]	581.00 (9.86)	574.00 (7.22)	a (12.12)	.58	-17.25	30.73	.18
IIV (ISD – Number Trials)	135.00 (8.41)	103.00 (6.16)	32.10 (10.66)	**.003**	11.64	52.56	.26
IIV (COV – Number Trials)	22.80 (1.23)	17.70 (0.90)	5.12 (1.54)	**.001**	2.14	8.10	.25
IIV (ISD – Letter Trials)	169.00 (7.94)	136.00 (5.82)	32.74 (9.39)	**.001**	13.41	52.06	.21
IIV (COV – Letter Trials)	27.40 (1.11)	22.00 (0.81)	5.36 (1.31)	**<.001**	2.67	8.04	.20

Abbreviations: COV: coefficient of variation; HC: healthy control; IIV: intra-individual variability; ISD: individual standard deviation; POMS: pediatric-onset multiple sclerosis; RT: response time

[a]controlling for age, sex, and parental education

Note. Sample sizes are reduced due to missing parental education data for one patient and seven HCs. RT is measured in milliseconds

Supplemental Table E. Group differences (POMS-HC) in whole brain DTI outcomes from the multiple linear regression presented as estimated marginal means

DTI Metric	POMS (n=30)	HC (n= 51)			95% Confidence Interval for effect estimate		
	M(SE)	M(SE)	B(SE)	*p*	Lower	Upper	Multiple R^2
Whole Brain FA (0 – 1)	0.188 (0.00)	0.194 (0.00)	-0.01 (0.01)	**<.001**	-0.01	-0.00	.20
Whole Brain MD ($10^{-3}mm^2$)	1.04 (0.01)	1.00 (0.01)	0.04 (0.01)	**.004**	0.01	0.06	.16
Whole Brain AD ($10^{-3}mm^2$)	1.21 (0.01)	1.17 (0.01)	0.04 (0.01)	**.01**	0.01	0.06	.16
Whole Brain RD ($10^{-3}mm^2$)	0.96 (0.01)	0.92 (0.01)	0.04 (0.01)	**.004**	0.01	0.06	.16

Abbreviations: AD: axial diffusivity; FA: fractional anisotropy; HC: healthy control; MD: mean diffusivity; POMS: pediatric-onset multiple sclerosis; RD: radial diffusivity

Note. Models were adjusted for age and sex; analyses were computed with lesions included in the diffusion-weighted images, as we were interested in the impact of pathology on whole brain microstructure

Supplemental Table F. Whole brain DTI metrics as correlates of CPT accuracy and fatigability in POMS patients (robust modelling)

DTI Metric	POMS (n=30) B(SE)	*p*	95% Confidence Interval for effect estimate Lower	Upper	Multiple R^2
Whole Brain MD ($10^{-3}mm^2$)					
IIV: ISD	92.59 (126.58)	.47	-117.13	302.31	.15
IIV: COV (%)	18.51 (18.25)	.32	-11.73	48.75	.20
Accuracy (% correct)	-8.14 (28.89)	.78	-58.97	42.69	.25
Mean RT	-53.83 (173.66)	.76	-342.67	235.02	.11
Whole Brain AD ($10^{-3}mm^2$)					
IIV: ISD	86.92 (123.27)	.49	-116.52	290.36	.15
IIV: COV (%)	17.48 (17.95)	.34	-11.87	46.83	.19
Accuracy (% correct)	-8.89 (27.44)	.75	-58.11	40.33	.25
Mean RT	-53.48 (167.55)	.75	-333.33	226.36	.11
Whole Brain RD ($10^{-3}mm^2$)					
IIV: ISD	95.12 (127.77)	.46	-117.37	307.60	.16
IIV: COV (%)	18.95 (18.33)	.31	-11.68	49.59	.20
Accuracy (% correct)	-7.67 (29.56)	.80	-59.21	43.87	.25
Mean RT	-53.69 (176.11)	.76	-346.52	239.14	.11

Abbreviations: AD: axial diffusivity; COV: coefficient of variation; IIV: intra-individual variability; ISD: individual standard deviation; MD: mean diffusivity; POMS: pediatric-onset multiple sclerosis; RD: radial diffusivity; RT: response time
Note. Models were adjusted for age, sex, and parental education

Supplemental Table G. Whole brain DTI metrics as correlates of CPT accuracy and fatigability in HCs (robust modelling)

DTI Metric	HC (n=51) B(SE)	*p*	95% Confidence Interval for effect estimate Lower	Upper	Multiple R^2
Whole Brain MD **($10^{-3}mm^2$)**					
IIV: ISD	7.17 (72.82)	.92	-151.17	165.51	.18
IIV: COV (%)	-6.31 (11.52)	.59	-31.02	18.41	.12
Accuracy (% correct)	-15.36 (19.93)	.45	-54.95	24.22	.06
Mean RT	263.64 (147.39)	.08	-58.37	585.65	.23
Whole Brain AD **($10^{-3}mm^2$)**					
IIV: ISD	1.67 (71.74)	.98	-155.64	158.99	.18
IIV: COV (%)	-6.76 (11.42)	.56	-31.30	17.78	.12
Accuracy (% correct)	-11.84 (19.52)	.55	-51.28	27.61	.06
Mean RT	243.65 (153.92)	.12	-77.73	565.02	.22
Whole Brain RD **($10^{-3}mm^2$)**					
IIV: ISD	9.88 (73.20)	.89	-148.35	168.10	.18
IIV: COV (%)	-6.03 (11.59)	.61	-30.74	18.68	.11
Accuracy (% correct)	-17.04 (20.07)	.40	-56.53	22.45	.07
Mean RT	271.50 (143.96)	.07	-49.63	592.63	.23

Abbreviations: AD: axial diffusivity; COV: coefficient of variation; HC: healthy control; IIV: intra-individual variability; ISD: individual standard deviation; MD: mean diffusivity; RD: radial diffusivity; RT: response time

Note. Models were adjusted for age, sex, and parental education