Characterizing the Neuropsychological Profile and Examining the Role of Cognitive Reserve in Pediatric-Onset Multiple Sclerosis Using a Computerized Battery

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Abstract

Multiple sclerosis (MS) is a chronic demyelinating and degenerative condition of the central nervous system. While the majority of affected individuals show their first symptoms between the ages of 25-35 years, 3-5% of people have a pediatric-onset (POMS) of the disease, with a first attack occurring prior to age at 18. POMS leads to a range of physical and cognitive symptoms that impact everyday functioning and development, however, further research is needed to understand the cognitive profile and predict outcomes.

The overall objective of this program of research was to better understand processes facilitating protection against the cognitive presentation of neuropathology in POMS, with a specific focus on cognitive reserve (CR) and its domain-specificity. Areas of deficit in POMS were first clarified, with delineation of dysfunction in speed and accuracy across cognitive domains using a computerized neurocognitive battery. In Study 1, we found that deficits in working memory, attention/inhibition, visuospatial processing, verbal recognition memory and verbal reasoning exist separately from and in addition to slowed speed of processing in individuals affected by POMS. Furthermore, we found that individuals with POMS are afforded some protection by CR (as estimated by parental education) in Study 2, however, these affects appeared weaker than what has been observed in adults. CR effects were strongest for tasks of executive functioning, where patients demonstrated greatest deficit relative to controls, and were not observed for tasks of information processing speed, potentially owing to differential availability of compensatory strategies in these networks.

These findings highlight differences in vulnerability to cognitive dysfunction in individuals with POMS, given impacts of the disease on developing functions and reserves. We propose that cognitive screening should be expanded beyond assessment of simple processing speed to identify a greater proportion of youth affected by the cognitive sequelae of MS. While the mechanisms contributing to the development of CR remain to be elucidated, engagement in a range of physically and cognitively enriching activities, as well as a focus on mental health may be helpful towards better cognitive outcomes for youth with POMS. Further research is needed with direct comparison to adults with MS to understand how the developmental context influences the profile of cognitive deficits and role of protective factors in POMS.

To Eugenie, who inspired a playful spirit of curiosity and fierce pursuit of knowledge

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ADEM	Acute disseminated encephalomyelitis
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
BICAMS	Brief International Cognitive Assessment for MS
BSMSS	Barratt Simplified Measure of Social Status
CIS	Clinically isolated syndrome
CNS	Central nervous system
CPDDS	Canadian Pediatric Demyelinating Disease Study
CR	Cognitive reserve
CSF	Cerebrospinal fluid
DMT	Disease modifying therapy
EBV	Epstein-Barr Virus
EDSS	Expanded Disability Status Scale
fMRI	Functional magnetic resonance imaging
HADS	Hospital Anxiety and Depression Scale
HC	Healthy control
IQ	Intelligence quotient
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
PCET	Penn Conditional Exclusion Test
PCNB	Penn Computerized Neurocognitive Battery
PI-ED	Pediatric Index of Emotional Distress
POMS	Pediatric onset multiple sclerosis
PPMS	Primary progressive multiple sclerosis
RRMS	Relapsing remitting multiple sclerosis
SD	Standard deviation
SDMT	Symbol Digit Modalities Test
SPMS	Secondary progressive multiple sclerosis

Chapter 1: Introduction

1.1 Overview of Multiple Sclerosis

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS), characterized by inflammatory and degenerative processes that lead to a range of progressive physical and cognitive symptoms. It is the most common inflammatory neurological disease affecting young adults, with the majority of affected individuals showing their first symptoms between the ages of 25-35 years, however, 3-5% of people with MS experience their first attack prior to age 18[1]. MS is estimated to affect upwards of 2.2 million people worldwide, with the highest prevalence rates found in North America (164 per 100 000 persons) and Canada in particular (150-180 per 100 000)[2].

Etiology. The precise mechanism by which MS develops remains uncertain, however, its etiology is thought to be explained by an interaction of genetic susceptibility and environmental exposures. Support for a genetic influence is evidenced by a concordance rate of 25% in monozygotic female twins, compared to 5% in dizygotic twins and 3% in siblings[3]. Moreover, about one in eight adults with MS, and one in six youth with pediatric-onset MS (POMS) report a family history of the disease[4, 5]. Genome-wide studies have identified more than 150 single nucleotide polymorphisms with potential association to MS, most of which are believed to be linked to immune function, but contribute only modestly to one's risk of MS[6, 7]. Greater evidence exists for risk associated with the *HLA-DRB1* gene, however, with heterozygotes and monozygotes for the *HLA-DRB1*15:01* allele showing odds ratios of >3 and >6 for MS, respectively[8]. The *HLA* gene has been implicated in several other infectious, autoimmune and inflammatory disorders, and is hypothesized to be associated with antigen presentation.

Migration studies provide strong evidence that MS susceptibility is largely mediated by early environmental exposures, with adult migrants retaining the risk of their home countries, while young migrants and children born to migrants take on the risk of the country migrated to[9]. Further, a month-of-birth effect[10] and a maternal parent-of-origin effect in half siblings[11] are suggestive that MS risk is partially modified in utero. According to Belbasis and colleagues[12], 44 environmental risk factors have been studied in relation to MS. Among these, exposure to the Epstein-Barr Virus (EBV) has shown the most consistent and significant associations to MS. Meta-analyses suggest that symptomatic EBV, as manifested by infectious mononucleosis, more than doubles the risk of MS[13]. Seropositivity for EBV is observed in nearly all adult MS patients, as compared to 90% of the general population[14, 15], and in 85% of youth with POMS, as compared to 40-45% of regional age-matched controls[16-18]. Notably, high titers of EBV antibodies predict

disease activity on MRI, as well as risk of conversion from the initial demyelination seen in clinically isolated syndrome (CIS) to definite MS[19, 20].

Apart from EBV infection, smoking exposure also shows robust associations to MS susceptibility[12]. Although the majority of studies have examined history of cigarette smoking in the individual with MS, there is also evidence for risk associated with passive smoke exposure[21]. Dose-response relationships have been observed for both MS susceptibility and disease progression, suggesting the role of cigarette smoke on MS may continue beyond MS-onset[22]. Cigarette smoke may exert its influence via effects on the immune system, demyelination, and/or disruption of the blood-brain barrier, however, these mechanisms remain speculative[12, 22]. Associations have been found between organic solvents and MS susceptibility[23], but not for tobacco snuff use[24], suggesting that the mechanism of action may be initiated through the lungs. Similarly, recent studies have indicated exposure to air pollutants (including particulate matter, carbon monoxide, nitrogen oxides, sulfur dioxide, ozone, and heavy metals) as a potential contributor to one's risk for MS development and relapse[25].

Women appear to be at least twice as likely to be diagnosed with MS than men, however, this sex difference occurs only for MS-onset that follows puberty[26], suggesting a role of gonadal hormones on the development of MS. MS disease activity also varies as a function of hormonal changes related to menstruation and pregnancy, with fewer relapses during pregnancy and increased risk during the three months post-partum[27, 28]. Interestingly, the female to male sex ratio of MS is steadily increasing in most developed countries, and appears to be driven by a disproportional increase in incidence of MS in women, however, the reason for this change in incidence remains unclear[29].

Finally, low vitamin D levels and reduced exposure to sunlight have also received attention as potential risk factors for MS[30], to help explain the latitude gradient in MS prevalence observed historically. Greater risk has been associated with living farther from the equator, or in locations where there is reduced sunlight exposure; however, this gradient has reduced in recent years[31]. Still, low serum vitamin D is observed in youth and adults affected by MS[5], and early trials for vitamin D treatment show some promise for reductions in MS disease markers and relapse rate[30], leading to recommendations for supplementation in people with MS.

Pathophysiology and MRI features. MS was originally named '*sclerose en plaques'* in reference to the demyelinating plaques observed by Charcot in the periventricular area, pons and spinal cord[32]. Since then, MS has been largely characterized by its multiple foci of inflammation associated with axonal scarring and neurodegeneration in the brain and spinal cord.

Although its exact pathogenesis remains unclear, MS has traditionally been conceptualized as an autoimmune disorder, whereby peripheral immune cells are activated and cross the blood-brain barrier, attacking the myelin of the CNS. More recently, this '*outside-in*' model of MS has been contrasted with an '*inside-out*' model by Stys and colleagues[33], which purports that MS may be a neurodegenerative disease at its outset. In this model, primary degeneration is believed to occur in the oligodendrocytes and myelin, and products of these degenerative processes are hypothesized to trigger an autoimmune response, which varies according to the individual's immune priming.

Most typically, MS inflammation occurs in an episodic fashion at its outset, with the infiltrate dominated by T-lymphocytes, but including also B-cells and plasma cells in lower numbers[34]. These episodes are associated with gadolinium-enhancing perivascular lesions on MRI, suggestive of breakdown of the blood-brain barrier. While there appears to be relative sparing of axons early in the disease, as well as several neuroprotective pathways that help to preserve cell function, more substantial damage and/or recurrent injuries lead to permanent axonal and neuronal damage, occurring through oxidative stress, mitochondrial injury and subsequent ion channel dysfunction[35]. These pathways ultimately contribute to cell death and axonal loss, mediated by apoptosis and Wallerian degeneration[35]. Previously active lesions may thus remain visible on T2 and T1-weighted MRI, with the extent of T1 hypointensity correlating with the magnitude of tissue destruction[34, 36].

Some lesions – termed *smoldering plaques* – remain chronically active following this acute stage, and may expand further as a result of sustained inflammatory processes driven by a rim of activated microglia and macrophages surrounding the inactive lesion core[37, 38]. These lesions are more characteristic of progressive stages of MS, wherein chronic inflammation appears to be trapped within the blood-brain barrier of the CNS, and has a greater proportion of B-cells and plasma in the infiltrate[39, 40].

Importantly, although MS neuropathology is most clearly evident in the white matter on MRI, demyelination, axonal injury and neuronal death also occur in the grey matter of the cortex, cerebellum and deep nuclei, as well as in normal-appearing grey and white matter[34, 41]. Together, this accumulation of focal and diffuse neuropathology contribute to global atrophy, as reflected by widening of the ventricles and enlargement of the outer meningeal cerebrospinal fluid (CSF) spaces[34].

Cortical lesions have been classified into three types: leukocortical (involving deeper layers of grey matter and adjacent white matter), intracortical (centered on blood vessels and confined within the cortex), and subpial (extending from the pial surface into the cortex)[42]. These lesions show a

marked topographic distribution, with greater involvement of the cingulate gyrus, frontal, temporal, insular and cerebellar cortices, as well as in the hippocampi.

The pathogenic mechanisms leading to damage in the cortex are still under investigation, however, many appear to overlap with that which is seen in white matter[42]. Conversely, subpial lesions appear to be initiated by inflammatory infiltrates diffusing from the meninges, while leukocortical lesions may in part reflect secondary degeneration arising from adjacent transected neurons in the white matter[42, 43]. Damage to normal-appearing white and grey matter appear mediated by more diffuse inflammatory processes, as well as Wallerian degeneration[34, 44].

Notably, volume loss appears to occur more quickly in deep grey matter structures than in other regions of the brain across MS subtypes, with particular susceptibility of the thalamus[45, 46]. This vulnerability of the thalamus is attributable, in part, to its extensive connectivity to cortical grey matter regions, leading to more significant degeneration from axonal transection of white matter tracts projecting to and from this structure[41]. Moreover, two types of lesions have been observed in the thalamus – perivascular ovoid lesions and diffuse periventricular lesions – suggesting vulnerability to more than one pathologic mechanism[47, 48]. With this heightened sensitivity to MS neuropathology and its robust associations to clinical outcomes, the thalamus has been put forward as a promising holistic MRI proxy for neurodegeneration[46, 47].

Diagnostic criteria. The diagnosis of MS requires careful integration of clinical, imaging, and laboratory findings to confirm the dissemination of lesions in space and time, and to ensure no other explanation better fits the clinical presentation. The 2017 McDonald criteria define what is needed to meet criteria for dissemination in space and dissemination in time[49]. These criteria are utilized primarily (but not exclusively) in the context of a CIS. CIS is defined as *a monophasic clinical episode with patient-reported symptoms and objective findings that are indicative of a focal or multifocal inflammatory demyelinating event in the CNS, developing acutely or subacutely, with the duration of at least 24 hours, with or without recovery, and in the absence of a fever or infection*.

Dissemination in space can be demonstrated by one or more T2-hyperintense lesions in two or more of four areas of the CNS: periventricular, cortical or juxtacortical, infratentorial brain regions, or the spinal cord. Dissemination in time can be demonstrated by the simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time, or by a new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan. Importantly, the presence of oligoclonal bands in the CSF may be substituted for the requirement of fulfilling dissemination in time for cases with typical CIS, fulfilment of dissemination in space, and no better explanation for the clinical presentation.

Primary progressive MS can be diagnosed in people with one year of disability progression (determined retrospectively or prospectively) and two of the following: (1) one or more T2-hyperintense lesions in the above-mentioned regions characteristic of MS; (2) two or more T2-hyperintense lesions in the spinal cord; or (3) presence of CSF-specific oligoclonal bands. At this time, clinical symptoms are required for a presentation to be considered MS; radiologically-isolated syndrome, which is characterized by incidental MRI findings consistent with MS, does not meet criteria, though it is recommended that these individuals be followed closely.

Clinical course. The course of MS moves through several stages, from being at-risk, through subclinical prodromal and subsequent relapsing and/or progressive phases. Formally, there are three major classifications for MS disease course, including: relapsing-remitting (RRMS), primary progressive (PPMS), and secondary progressive MS (SPMS). CIS was added more recently, referring to the first episode of potential MS[50, 51].

RRMS is the most common MS phenotype, found in approximately 85% and >98% of adults and youth with MS, respectively. This stage is characterized by relapses of new neurologic symptoms or worsening of existing symptoms, interspersed with periods of relative clinical stability. Relapses typically develop subacutely over hours to days, reach a plateau lasting several weeks, and then gradually recover[6]. Full recovery from relapses often appears complete in early MS; however, many leave residual deficits. Over time, these deficits begin to accrue, leading to sustained disability and transition into a secondary progressive stage.

SPMS is phenotypically varied, with periods of progression superimposed with possible relapse activity and periods of relative stability. Determination of the onset of SPMS is difficult, with initial progressive symptoms typically presenting in a subtle and fluctuating manner[52]. This diagnosis is often established retrospectively, based on clinical evidence of accumulating disability over a period of at least 6 to 12 months[50]. As the disease progresses, however, the clinical course increasingly takes a progressive form, with fewer bouts of acute inflammatory activity. The median time to conversion to SPMS ranges from 10-19 years from RRMS onset[53, 54], with shorter time to conversion for individuals with a higher age at onset, male sex, spinal cord symptoms, and incomplete relapse recovery[53].

Finally, PPMS is characterized by a lack of initial relapsing and remitting phase; however, progression is not necessarily uniform, and superimposed relapses, as well as periods of relative stability, are possible. This variant is observed in approximately 10-15% of cases[55], with a gradual accrual of disability typically involving one dominant neuronal system. Notably, PPMS is virtually unheard of in children, and the age at onset is on average 10 years older for PPMS relative

to RRMS (40 years vs 30 years); this age at onset is more similar to that which is found in SPMS[55].

Importantly, the delineation between MS subtypes exists primarily at a clinical level, with histological differences occurring mostly in proportion. As such, MS might rather be considered as a continuum of disease, extending from prodromal (i.e., radiologically isolated disease) to relapsing ('inflammatory dominant') and progressive ('neurodegeneration dominant') stages[6].

Clinical features. MS can manifest with a variety of physical and/or cognitive symptoms, depending on what areas of the CNS are affected. Patients will typically present with motor, sensory or visual symptoms at the time of their first attack. Although it is also possible for patients to present initially with cognitive symptoms, this is far less common, with cognitive challenges more typically developing gradually over time.

Common MS symptoms occurring at onset include unilateral optic neuritis, double vision, numbness or tingling, dizziness and vertigo, muscle spasticity or weakness, gait difficulties, pain, bladder problems, and sexual dysfunction[56]. These symptoms have a relapsing-remitting course in RRMS, but then accumulate and/or worsen as the disease progresses, leading to more significant disability. The extent of neurological disability is typically monitored using the Expanded Disability Status Scale (EDSS), with scores ranging from 0 (no disability) to 10 (death due to MS)[57].

In addition to the physical challenges contributing to disability in MS, fatigue is one of the most common symptoms, affecting up to 83% of patients, and is reported to be the most significant contributor to a reduced quality of life[58]. MS-related fatigue is differentiated from that experienced by healthy persons in that it is persistent, as well as sensitive to heat[59-61]. Several mechanisms have been proposed to contribute to the development of fatigue in MS, including primary disease processes of inflammation and neuronal injury[58]. Fatigue may also develop secondarily to poor sleep, medication, lack of physical activity, cognitive exertion, pain and/or depression[62].

Psychiatric symptoms are also significant contributors to quality of life in MS. Depression affects up to 50% of adult patients over the course of their lifetime, and is associated with increased morbidity and mortality[63]. Risk for depression is increased for individuals reporting greater stress, use of emotion-focused and avoidant coping strategies, dissatisfaction with their social supports, and negative conceptions of themselves and the illness (e.g., feelings of helplessness, lack of control, expectations for poor outcome)[64]. However, inflammatory activity may contribute directly to one's risk for depression, as shown in MS and other populations[65].

Anxiety is also common in MS, affecting approximately 22% of patients. Anxious symptoms typically present as panic disorder, obsessive compulsive disorder or generalized anxiety disorder[66, 67].

Treatment. The treatment of MS typically includes corticosteroids for acute relapses, immunomodulatory disease-modifying therapies for long-term suppression of disease activity, and supplemental interventions for the management of symptoms (such as fatigue, pain, depression, spasticity). Although comparatively less is known about the effect of MS treatments in POMS, the pharmacological approach is similar to that for adult-onset MS, with demonstrated safety and tolerability of first-line treatment regimens in POMS[68]. As such, it is recommended that disease-modifying therapies are initiated soon after the diagnosis is confirmed[69, 70].

High dose and short-term oral or intravenous steroids (methylprednisone) are recommended for the management of acute disease activity[68, 71]. IVIg or plasmapheresis may be utilized in the case of treatment failure[68]. For subsequent and ongoing management of MS, disease-modifying therapies are applied with the goal of preventing future relapses, slowing disease progression, and reducing lesion accrual. The first-line of disease-modifying therapies include: glatiramer acetate (Copaxone), interferon beta-1a (Avonex, Plegridy, and Rebif), interferon beta-1b (Betaseron and Extavia)[68, 72]. These therapies have shown efficacy and tolerability in POMS, however, poorer treatment outcomes are more common in youth with MS and may lead to the use of second-line therapies[68, 73]. Second-line therapies include: natalizumab (Tysabri), fingolimod (Gilenya), teriflunomide (Aubagio), dimethyl fumarate (Tecfidera), alemtuzumab (Lembtrada), and mitoxantrone (Novantrone)[72, 74].

In addition to pharmacological treatments for management of disease activity and MS symptoms, it is recommended that a number of lifestyle-based behavioural changes are also considered. These include smoking cessation, dietary changes, management of comorbid cardiovascular disease, and increased physical activity[75]. Physical therapies may be considered to improve mobility, muscle strength and aerobic capacity, as well as to reduce fatigue[76]. Moreover, psychotherapy – including cognitive behavioural therapy, mindfulness-based interventions, acceptance and commitment therapy, or motivational interviewing – may be helpful for improving mental well-being in the context of comorbid depressive or anxious symptoms[76-79].

1.2 Pediatric MS

Approximately 3-5% of people affected by MS have an onset prior to age 18[1], with an annual incidence in the range of 0.07-0.29 per 100 000 children[80]. The onset of POMS typically occurs during adolescence, but can also occur below age 10 and has been observed as low as 2 years of age. As mentioned previously, the female preponderance for MS is only observed after puberty, with the female:male ratio appearing more equal in patients younger than 10-12 years of age[80].

Most children present with similar symptoms to those which are seen in adults, including optic neuritis (10-22%), motor dysfunction (30%), sensory symptoms (15-30%), ataxia (5-15%), and brainstem symptoms (25%)[81]. Diagnosis of POMS is based on the same criteria as that which is used in adults (described above), however, special consideration is needed when applying these criteria to children younger than 11 years of age. Younger children are more likely to present with polyfocal deficits and encephalopathy, appearing more similar to acute disseminated encephalomyelitis (ADEM;[82]). ADEM is more common in children overall, relative to adults, and represents an important differential diagnosis to be distinguished from MS. A second clinical attack that is characteristic of MS is thus required for a diagnosis of MS to be given in the case of ADEM-like presentation at onset[83].

POMS is almost exclusively of the relapsing-remitting subtype (>98%), with fewer than 2% of children and adolescents showing a primary progressive presentation[84]. POMS appears more inflammatory than adult MS, with a higher number of enhancing lesions and greater frequency of relapses in the first few years following onset[85-87]. These relapses may be more severe in POMS, but subsequently show a fuller recovery, with the majority of patients returning to EDSS or Functional System Scores of zero[88, 89]. Younger patients also show greater reduction in the number of T2 lesions on scans serially, relative to older POMS patients[90]. In line with this fuller recovery from relapses, the time to conversion to SPMS is longer in POMS than in adults with MS (20 versus 10 years)[84]; however, this stage is ultimately reached at a younger chronological age[91].

Children with MS show greater involvement of the infratentorial white matter, particularly in the brainstem, relative to adults with similar disease duration[85, 92]. In the supratentorial region, POMS patients also show a smaller fraction of T2-hyperintense lesions that also appear as T1-hypointense lesions relative to adults, however, this ratio is more similar in the infratentorial region[92]. Given that myelination proceeds along a caudorostral gradient, it has been proposed that there may be a preferential immune targeting of mature myelin infratentorially in POMS. Moreover, it is possible that primary myelination occurring supratentorially during childhood and

adolescence may serve to reduce T1 lesion load and facilitate recovery post-relapse. Notably, youth with MS have shown smaller head size compared to age and sex-matched controls, suggesting that the onset of MS during this maturational period may affect brain and skull growth[93]. Smaller thalamic volumes are also observed in POMS, and appear to be associated in part with a failure of age-expected growth[94].

Similar to adults with MS, children and adolescents with POMS experience fatigue, depression and anxiety to a greater extent than their peers[95-97]. Clinically significant fatigue is typically reported in the range of 30-50% of youth with POMS[96, 98, 99], and can be of sufficient severity to require alterations to school programming[98, 100, 101]. Moreover, elevated symptoms of depression are reported in 15-30% of affected youth, while 5-34% of youth with POMS report elevated symptoms of anxiety[95, 96, 99, 102-105]. In addition to these internalizing presentations, emotional distress can be manifested as disruptive or aggressive behaviours in children and adolescents[106]. Although internalizing presentations appear more common in youth with POMS[96], elevated symptoms of inattention/hyperactivity and aggression are reported by parents in 16-48% and 8-23% of these youth, respectively[96, 101, 104].

Importantly, although many of the challenges contributing to difficulties with psychosocial adjustment likely overlap with adults with MS, the reasons for and implications of such difficulties in youth also differ. These younger people with MS are navigating different social systems and are striving for different developmental goals, such as having a sense of belonging with peers and developing autonomy as they move into young adulthood[107, 108].

As in adults with MS, these different sequelae of MS are often interrelated. Fatigue can contribute to everyday challenges and in turn lead to or exacerbate low mood, anxiety and cognitive/academic development; fatigue may arise secondarily to depressive states, persistent anxiety and/or cognitive load; or these symptoms may together be predicted by common underlying disease mechanisms. Moreover, the impact of MS to brain systems implicated in self-control may have implications for emotional and behavioural regulation that contribute to social and emotional difficulties.

Notably, the frequency and/or severity of fatigue, mood and anxiety symptoms often differ between self- and parent-reports, with parents consistently endorsing a larger number of or more severe symptoms. This could reflect a pattern of under-reporting in youth, which may be related to lack of insight and/or desire not to be differentiated from peers[96, 107, 109]. It has also been proposed that parental reports could be confounded by parental sadness for the ‘loss’ of a healthy child, or anticipated losses that their child may experience related to MS[96]. Importantly, discrepancies between self- and parent-reports indicate that these measures may capture different

aspects of the experience of living with MS, and highlight the need for collection of data from both sources when possible.

1.3 Cognitive symptoms

Cognitive impairment occurs in 22-53% of individuals with POMS, depending on the sample characteristics, as well as the methods for measurement of cognitive function and determination of impairment[101-103, 110-119]. Although the patterns of cognitive dysfunction vary across individuals with POMS, deficits are most consistently observed in complex attention, information processing speed and visuomotor integration[95, 100-103, 113, 114]. People with POMS also frequently demonstrate deficits in executive functions, visuospatial ability, and verbal and visual learning and memory[95, 97, 100, 101, 120, 121]. Executive dysfunction has been primarily observed on tasks of working memory[97, 100, 101, 103, 110, 113, 115, 120], and is reported by parents in the context of everyday metacognitive behaviours[97]. Conversely, performance on tasks of cognitive flexibility and planning appear less affected in POMS[97, 100, 102, 110]. Visuospatial deficits are shown on tasks of copying/construction and puzzle-completion[95, 100-102, 115]. Conversely, deficits in nonverbal problem-solving are less consistent across studies[95, 100-102, 113, 115, 121].

Youth with MS are at risk of impairment in verbal abilities, including expressive and receptive language, and verbal fluency[100, 102, 103, 122, 123]. Expressive deficits have been observed for tasks of naming, expressive vocabulary, verbal reasoning, and general knowledge. Receptive deficits have been observed for tasks of listening comprehension – including tasks where they must answer questions about information that is read to them, or follow increasingly complex sets of verbal instructions. Impairments in verbal fluency are less consistent across studies, but have been seen for both phonemic and category fluency[95, 100-102, 115, 120]. Notably, difficulties with language are not typically observed in adults with MS, aside from deficits in confrontation naming and verbal fluency[124].

More recently, studies of cognitive function in MS have begun to examine social cognition, which refers to the mental operations that underlie social interactions. Youth with POMS demonstrate poorer performance on both affective (Reading the Mind in the Eyes) and cognitive theory of mind tasks (Faux-Pas Test, First- and Second-Order False Beliefs) relative to controls[125]. This pattern is generally similar to what has been observed in adults with MS, with deficits observed in theory of mind and facial emotion recognition[126].

Longitudinal studies of cognitive function in POMS illustrate a more complex and variable picture than cross-sectional studies, as relapses occur and attacks are repaired, disease burden is

accrued, and these youth progress through maturational improvements in cognitive function. While youth with POMS can demonstrate improvements in cognitive function over time when examining raw scores[127, 128], declines in age-adjusted scores have been observed, suggesting a lack of age-expected maturation at a group level[95, 120, 129]. Importantly, case studies illustrate that youth with POMS can also show deterioration relative to their own prior level of functioning[120, 130]. Moreover, several studies highlight individual variability in trajectories of cognitive development, with subsets of participants showing declining, stable, or improving age-adjusted cognitive scores over time[110, 114, 122, 130]. Comparisons between adults with POMS and adult-onset MS show poorer performance for POMS patients on a task of information processing speed that were retained after adjusting for age and disease duration[131]. These results suggest that cognitive challenges may not only increase as the disease progresses, but individuals with POMS may be at greater risk for long-term cognitive challenges due to an early onset of the disease.

Impacts to everyday functioning. The cognitive dysfunction and disruptions to schooling occurring as a consequence of POMS appear to be of sufficient severity to have implications for academic and daily functioning. School activities are impacted for upwards of 30% of youth with POMS, with reports of difficulties maintaining focus in class, needing special assistance, reducing course load, grade retention, and in some cases school drop-out[100, 103, 110]. These academic challenges may have long-term consequences for academic attainment, as fewer adults with POMS show high educational attainment relative to those with adult-onset MS, and relative to what might be expected based on their parent's level of education[132].

With regards to specific academic abilities, youth with POMS are at greater risk of having difficulties with language, as well as reduced general and word knowledge, as described above. Moreover, youth with POMS show poorer performance on tasks of word reading, spelling and math calculation, with the latter showing associations to processing speed and white matter integrity[133]. These deficits are not consistently replicated across studies, however[95, 100, 113].

Engagement in hobbies and sports, and relationships with family and peers are also reported to be affected in 41% and 28% of youth with POMS, respectively[110]. Poorer adaptive skills have also been reported by parents of children with POMS relative to parents of controls, while youth with POMS self-report poorer self-reliance, suggesting that these youth feel a lower sense of confidence in their ability to make decisions, solve problems, and/or be dependable relative to their peers[96]. Although other aspects of MS surely contribute to these everyday impacts of POMS (including physical disability, fatigue, psychiatric symptoms, and changes in

psychological outlook), several of these outcomes correspond closely to incidence of cognitive impairment[103, 110].

Assessment of neuropsychological function in POMS. The neuropsychological deficits observed in POMS have been measured through a variety of assessment tools over the years, including primarily traditional paper-and-pencil tasks administered under a standardized set of testing conditions, but also behavioural reports such as the Behavioural Rating Inventory of Executive Functions, and computerized measures such as the Cogstate Brief Battery.

Portaccio and colleagues[115] were the first to propose a set of neuropsychological tests to screen for cognitive dysfunction in POMS, titled the Brief Neuropsychological Battery for Children with MS. This battery includes measures of: vocabulary (Wechsler Intelligence Scale for Children-Revised), sustained attention and working memory (Symbol Digit Modalities Test [SDMT], Trail Making Tests), and verbal learning and recall (Selective Reminding Test immediate and delayed). These tasks were found to have 96% sensitivity and 76% specificity in discriminating cognitive impairment as defined through a full neuropsychological battery (including measures of visuospatial learning and recall, cognitive flexibility, verbal fluency, and expressive and receptive language), which identified cognitive impairment in 41% of POMS participants based on criteria of failing (<5th percentile of the healthy control [HC] group) on four or more of a total of 17 tests.

The Brief International Cognitive Assessment for MS (BICAMS) is an assessment battery developed by an international committee to detect cognitive deficits in adults with MS. The BICAMS is comprised of: the oral SDMT, the learning trials from the California Verbal Learning Test-second edition or the Rey Auditory Verbal Learning Test, and the Brief Visual Memory Test-Revised. This tool was applied in POMS by Charvet and colleagues (2018), and was found to differentiate between POMS and HC groups, classifying 26% of patients as cognitively impaired based on the criteria of failing one test (scoring below -1.5 standard deviations from the mean).

The SDMT is the most widely used measure of cognitive function that has been applied in adults and youth with MS, and has in itself been proposed as a screener for cognitive impairment. This tool measures the speed at which one can identify the appropriate numbers to match to symbols, according to how they are paired in a key. In the traditional paper-and-pencil version, participants are asked to write the appropriate number that goes with each symbol on the page. The SDMT has also been adapted to remove motor demands, by asking participants to provide the appropriate numbers orally. The number of correct responses provided within 90 seconds is recorded as their raw score.

The SDMT is primarily classified as a task of sustained attention and information processing speed, although it also relies on visual scanning and perception, decision making, error processing, and visual working memory. It has been deemed an adequate screener for cognitive dysfunction in POMS, differentiating between youth with POMS from pediatric patients with other neurological disorders, as well as from HCs[111]. The SDMT has shown 77% sensitivity and 81% specificity to detecting cognitive impairment based on a larger battery (with scores at least one SD below the mean on at least one-third of the tests administered). Concordance was even greater for participants completing the SDMT and neuropsychological battery closer in time.

The SDMT has gained this ubiquity due to the prevalence of slowed processing speed in MS. Slowed information processing is one of the most robust cognitive findings in adults and youth with POMS, and is believed to arise as a consequence of the widespread loss of integrity of white matter pathways[134]. Slowed performance on the SDMT is indeed associated with structural MRI measures of MS neuropathology that are reflective of widespread white matter injury, including smaller volumes of the thalamus, as well as lower fractional anisotropy values in hemispheric, corpus callosum and thalamic regions in POMS[97, 102, 135].

Importantly, information processing speed is implicated in the effective functioning of other cognitive domains. For instance, reduced efficiency may interfere with the learning of new information, and with the coordination of parallel cognitive processes in tasks requiring greater cognitive demand, as proposed by the *Limited Time Mechanism*[136]. In fact, it has been proposed that slowed processing speed may represent a fundamental deficit in MS, that in turn leads to inefficiencies – and ultimately deficits – in a range of cognitive functions[137]. This theory is termed the *Relative Consequences Model*, and is evidenced by associations between processing speed and performance on tasks of executive function and social cognition[138, 139], as well as by reductions in group differences on tasks of executive function and memory after adjusting for information processing speed either statistically or in task demands in adults with MS[140-146]. Some deficits, however, appear to exist over and above deficits in information processing speed, such as for social cognition in POMS [125]. Whether slowed processing speed is indeed a driving factor in the profile of neurocognitive deficits in MS remains unclear, and warrants further investigation in individuals with POMS in particular, given potentially differential relationships between domains of cognitive functioning in this developmental cohort.

In recent years, there has been a growing interest in computerized tools for neuropsychological assessment, which offer efficient and standardized measurement of cognitive function on an interface that is user-friendly for children and adolescents. Importantly, these tools

facilitate the measurement of both accuracy and response time, allowing for delineation between performance that is impaired as a result of or independently from slowed processing speed.

One such tool that has been applied in the context of POMS is the Cogstate Brief Battery, which consists of three speeded processing tasks: Detection (measuring processing speed), Identification (measuring continuous visual attention), and One-Back (measuring speeded working memory). Differences between POMS and HC groups were found for Detection and Identification, but not for the One-Back. Rates of impairment were similar between the Cogstate and BICAMS (27% and 26%, respectively), with overlap in classification in 74% of cases (69% in POMS and 85% in HCs;[112]). The Cogstate was proposed to be relatively more sensitive to subtle impairments in cognitive processing, given its targeted assessment of information processing functions.

Another available computerized battery is the Penn Computerized Neurocognitive Battery (PCNB), which includes a set of fourteen computerized tests evaluating function across five broad domains: executive functions (attention, cognitive flexibility, working memory), episodic memory (verbal and visual recognition), complex cognition (verbal reasoning, nonverbal reasoning, visuospatial processing), social cognition, and sensorimotor speed[147, 148]. This battery was developed using tests previously validated with functional neuroimaging[149], and has shown adequate reliability and validity for use in children and adults[147, 150]. The PCNB has also been applied to a variety of clinical populations, effectively differentiating neurocognitive profiles between controls and people with chronic kidney disease, 22q11.2 deletion syndrome, mood disorders, and exposures to herpes simplex virus or hepatitis C[151-155]. With separate measures for accuracy and response time across a breadth of cognitive domains, the PCNB may offer new insights on the neurocognitive profile of POMS.

Management of cognitive symptoms. Our understanding of how to prevent or manage the cognitive deficits associated with POMS is still limited. To date, there are no approved pharmacological treatments for cognitive impairment in MS. The majority of early clinical trials for disease-modifying therapies did not include cognitive endpoints. Moreover, while there is some limited evidence for beneficial effects of disease-modifying treatments for cognitive outcomes, these findings remain confounded by practice effects[156-158].

With regards to behavioural approaches, some promise has been shown for cognitive rehabilitation in adults with MS. Cognitive interventions may vary in their target and approach, with some focusing on remediation of cognitive function through process-training, while others focus on teaching compensatory strategies to facilitate adaptation to deficit. Few interventions have met

criteria for practice standards in the field, however, due to a lack of replication of treatment effects, active control groups, adequately powered samples, a significant follow-up period for testing, differentiation of near and far-transfer of cognitive effects, and a consideration of individual differences[159]. Currently, the strongest evidence exists for memory strategy training via the modified Story Memory Technique, and for computerized attentional training through the Attentional Process Training program.

Evidence for effective approaches to cognitive rehabilitation in POMS are even more sparse[160-162]. As a result, the cognitive symptoms of POMS are more typically managed on a case-by-case basis. Specific accommodations may be recommended to support these youth at home and at school, depending on the youth's area of need. Further research is thus needed to determine effective approaches to prevent, accommodate, or remediate cognitive dysfunction.

Predictors of cognitive outcome. Cognitive dysfunction in POMS is predicted in part by a younger age at disease onset, longer disease duration and greater neurological disability, however, these findings are not consistently found across studies[95, 97, 100-103, 110-114, 118, 120, 121, 127, 129, 163]. Till and colleagues[97, 102] found associations between age at onset and the majority of cognitive outcomes were washed out after adjusting for disease duration. More consistent have been associations between an earlier onset and poorer expressive vocabulary[102], as well as worse longitudinal trajectories of SDMT and visuomotor integration performance[127, 128, 131]. Youth with POMS and a younger age at disease onset also show poorer performance on tasks of calculation, reading and spelling, suggesting potential impacts of early disruptions to schooling on the development of academic skills[133]. Associations between cognitive dysfunction and symptoms of low mood and fatigue have also been observed, though somewhat inconsistently[95, 99, 101-104, 164].

MRI measures of MS pathology show comparatively stronger associations with cognitive outcomes in POMS, with *r*-values ranging from 0.30-0.63 for measures of whole-brain T1 and T2 lesion, normalized whole-brain, frontal lobe, and corpus callosum volumes[97, 102, 163]. Thalamic volumes, in particular, seem to demonstrate robust associations, accounting for up to 51% of variability in cognitive outcome (i.e., *r*-values > .60)[97, 102, 163]. Importantly, despite the relative efficacy that MRI metrics offer in predicting cognitive outcomes, much of the variability in cognitive function remains unaccounted for. Moreover, a majority of youth and young adults with POMS appear to remain cognitively preserved despite accruing MS neuropathology[165]. This disconnect between disease burden and cognitive function has been observed in adults with MS and has been

termed the '*cognitive-pathologic dissociation'*, leading to the question of how some individuals can better withstand MS pathology without cognitive impairment[166].

1.4 Cognitive reserve theory

In 2002, Stern first summarized theories of brain and cognitive reserves (CR), which posit that individuals will vary in the clinical expression of neuropathology due to differences in brain structure and function[167]. Brain reserve is a passive and quantitative model, wherein differences in brain size – believed to reflect the number of neurons and synapses – are proposed to account for differences in clinical outcome for individuals with comparable levels of neuropathology. Cognitive deficits are then proposed to arise once a certain threshold of pathology is met. Brain reserve is typically estimated by generalized measures, such as intracranial volume, however, more recent studies have incorporated more fine-grained measures, including specific patterns of grey matter volume, cortical surface area, cortical thickness, positron emission tomography measures of synaptic integrity, or white matter microstructure[168].

Conversely, Stern defines CR as *the adaptability of cognitive processes that helps to explain differential susceptibility of cognitive abilities or day-to-day function to brain aging, pathology, or insult*[168]. In other words, CR is an active model wherein individuals vary in the expression of neuropathology as a consequence of differences in capacity to adapt to insult. This is believed to occur through two neural mechanisms: neural reserve and neural compensation[169].

Barulli and Stern describe neural reserve as differential efficiency and/or capacity of task-related networks[169]. Network efficiency is the extent to which a network needs to be activated in order to complete a given task, with more efficient networks requiring less activation to produce the same level of performance. Network capacity is the extent to which activation can be upregulated with increasing task difficulty. Healthy individuals with better task performance typically show greater network efficiency for that task, which in turn gives a larger dynamic range for upregulation with increasing demand[170]. In the context of brain injury, these individual differences in neural reserve are believed to lead to differential capacities to engage task-related networks in a compensatory fashion.

Conversely, neural compensation refers to the maintenance of functionality through the use of alternate networks – and thus cognitive strategies – when primary task-related networks are compromised. Individuals with higher CR may have more varied approaches to solving a problem, and thus be able to flexibly invoke these strategies in the context of injury to brain structures typically activated when completing a task[169].

CR is believed to be determined by innate factors (genetics, in utero exposures), as well as lifetime exposures, such as one's participation in physically and cognitively stimulating activities[171]. As such, CR is often measured proximally by sociobehavioural determinants, including years of education, crystallized intelligence, occupational complexity, socioeconomic status, and engagement in cognitive leisure or physical activities. Other approaches to measuring CR include summary proxies (which capture a combination of the above-mentioned proxies), quantifying residual variance in cognition unaccounted for by demographic and brain predictors, and identification of resting-state or task-related functional activation of brain networks that may underlie CR[168].

Importantly, more recent models of reserve highlight the potential for brain structure to be influenced by experience. Interactions between brain reserve and CR are noted, as heritable components of brain structure can influence lifetime experiences, and engagement in enriching activities can lead to structural changes in the brain[169]. The concept of brain maintenance has been added to these models, which refers to individual differences in neuroprotective or enhancing mechanisms that influence one's susceptibility to pathology[169]. Importantly, rather than helping to explain dissociations between measured pathology and cognitive outcome, brain maintenance expands reserve theory to illustrate the potential role of genetic and lifestyle factors in the preservation of brain structure. Notably, several of the proposed formative variables for brain maintenance overlap with those predicted to influence CR. These recent evolutions in reserve theory underscore the modifiable nature of reserve and encourage interventions to offset functional decline[171, 172].

Cognitive reserve in MS. Theories of reserve were initially proposed in the context of aging and dementia, however, Stern proposed that the concept of reserve should be relevant to any situation where the brain sustains injury, and should also extend to encompass variation in performance in healthy individuals, particularly with increasing task demands. These models have now been applied to several clinical populations, including traumatic brain injuries, Parkinson's Disease, and HIV-related dementia, thus supporting the validity of this construct in response to neuropathology more broadly[166, 173-175].

Evidence for models of reserve have been examined in some depth in adults with MS. Eighteen studies were summarized in a meta-analysis, which found moderate effects for CR for tasks of attention, processing speed, verbal and visual memory, verbal fluency, and inhibitory control in adults with MS[176]. CR has been estimated in a number of ways, including years of education, occupational attainment, vocabulary knowledge, engagement in cognitive leisure

activities, and composite measures – all of which have shown association to cognitive outcomes[177-202]. Greater education and literacy/vocabulary are also protective against MS-related *changes* in cognitive efficiency and memory over time [177-179], and of performance in these same domains in participants with secondary progressive disease[180].

Several studies have differentiated between passive (i.e., accumulated) and active (i.e., modifiable) aspects of reserve. Cognitive leisure activity (e.g., engagement in hobbies, reading) has been shown to contribute to cognitive status independently of lifetime enrichment, supporting the potential for modification to reserves later in life[181-183]. While some studies show similar but independent effects sizes across these reserve types [182, 183], others show stronger effects for passive reserve (education, occupation), relative to engagement in leisure activities[184]. Luerding and colleagues[185], however, found that the effects of CR activities (i.e., reading, physical activity, and challenging occupations) were stronger for MS participants with low education, relative to those pursuing higher education, suggesting that different avenues to bolstering reserve may be of relevance depending on one's accumulated CR.

Importantly, engagement in leisure activities appears to vary as a consequence of clinical and disease factors, with lower active reserve reported over time for MS participants with progressive disease (relative to RRMS), and with greater physical disability, fatigue and depressive symptoms[186, 203, 204]. In one study, depressive symptoms were found to account for 17% of variance in leisure activity (compared to 4.6% and 2.6% for education and physical disability), and associations between leisure activity and cognitive outcomes were no longer significant after adjusting for depressive symptoms[203]. Of note, Schwartz and colleagues[187] illustrated differences in psychological appraisals between MS participants with low and high CR – including a greater focus on positive and controllable aspects of their life in those with higher CR. It is proposed that mood symptoms may thus represent an important primary target to facilitating engagement in cognitive activities. Passive CR effects (i.e., accumulated lifetime contributions to CR), by contrast, appear robust to mood symptoms[188].

Proxies of CR have shown moderation effects with structural MRI measures of MS pathology, whereby higher CR attenuates the negative relationship between MS disease burden and cognitive outcome[177, 178, 183, 189-196, 205]. In other words, the negative impact of MS pathology on cognition is greater in persons with lower CR than in persons with higher CR. In one study by Rocca and colleagues[197], this type of interaction was shown specifically for thalamic volume, and not for other regional brain structures showing reduced volume in MS participants. Importantly, CR has been shown to protect against cognitive inefficiency independently of maximal

lifetime brain growth (a proxy for brain reserve), thus providing support for protective effects of lifetime experiences beyond the association between brain size and intellectual function[177, 205].

Mechanisms for CR have been examined in functional MRI (fMRI) research in adults with MS. Sumowski and colleagues[198] described a “CR network”, whereby MS patients with greater CR showed less recruitment of task-related regions and lesser deactivation within the default mode network during working memory processing. Notably, expression of this network almost fully mediated the relationship between CR and cognitive status, providing support for network efficiency as a mechanism for CR. In comparison to controls, cognitively preserved MS patients show enhanced patterns of activation on tasks of episodic memory, attention, and working memory [206-215]. This compensatory activity appears to vary as a function of structural damage, with larger magnitudes of activation shown for patients with larger lesion volumes or more significant grey matter atrophy[211, 212, 215].

Evidence also exists for a threshold effect, whereby patients demonstrating impaired cognitive performance show less task-related activation than those whose performance is intact[211, 213]. In line with this theory, protective effects of CR appear specific to MS patients with shorter disease duration (< 5 years), while associations between disease burden and cognition vary less as a function CR in those who have had MS for longer[193, 197, 200].

Together, these findings suggest that having greater CR may enhance the efficiency of networks involved in task processing, thus increasing the capacity for compensatory upregulation with increasing injury or task demands; however, these mechanisms may become exhausted once a certain threshold of injury is met[216]. Interestingly, increases in task-related brain activation have been associated with fatigue, and in the absence of behavioural decrement in MS patients, raising the question of whether compensatory activation may be linked to subjective experience of fatigue[217, 218].

Of note, concepts of reserve have also been applied to adults with MS as a part of a model to explain the presentation of MS relapses and clinical progression[219]. In addition to individual differences in reserve, CR is proposed to differ across regions of the CNS. Regions with more linear structures (such as the spinal cord and optic nerve) are proposed to have fewer redundancies and less capacity for organizational plasticity, leading to reduced masking of or adaptation to neuropathology. Conversely, relapses occurring in complex functional networks (such as those responsible for higher-order cognitive processes) are proposed to have greater resilience to MS-related injury, leading to subclinical presentations. As neuropathology is accumulated over time, compensatory mechanisms become insufficient, and the disease takes a progressive course –

similar to Schoonheim and colleagues' theory of network collapse[216]. At this stage, disability is accumulated and symptoms occurring during prior relapses may resurface.

Pediatric models of reserve. Research on cognitive and brain reserves has been comparatively limited in pediatric populations, and warrants further investigation as reserves may manifest differentially in response to pathology accrued during periods of neurocognitive maturation. Given the observation of poorer cognitive outcomes for youth with a younger age at brain injury across different clinical populations, it has been proposed that actively maturing networks are more vulnerable to insult[220]. Youth may also have less reserve to employ at first insult, due to a reduced opportunity to acquire alternate strategies to approaching a task. Early brain injury may further disrupt the *development* of reserves, reducing the potential for adaptation to later insult. Importantly, models of reserve in youth are made more complex by the proposition that there is greater potential for neuroplasticity in immature networks[221]. This may enable the brain to be influenced more strongly by environmental enrichment factors, thus increasing the relevance of CR proxies for predicting cognitive outcomes.

Several methodological challenges arise with the measurement of reserves in youth, as proxies used in adults are often not appropriate. Education level and occupational attainment are not suitable proxies of CR for children and adolescents, as most youth have yet to achieve their educational and occupational potentials. Similarly, typical estimates of premorbid intelligence quotient (IQ), such as measures of word knowledge, are confounded by age in pediatric cohorts. Instead, CR has been estimated by measures of premorbid learning problems[222, 223], post-insult cognitive ability[224, 225], and sociodemographic factors[127, 226].

Importantly, measures of CR which encompass post-injury and/or current cognitive ability may be confounded by the injury itself, leaving it unclear whether relationships to cognitive outcome represent much more than common variability across cognitive measures. Similarly, measures of brain reserve (e.g., maximal lifetime brain growth, estimated by intracranial volume) may be confounded by disease factors which disrupt brain growth, thus making it unclear to what extent correspondence to cognitive outcomes reflect contributions of heritable factors independently of disease processes. For example, youth with MS demonstrate smaller intracranial volumes relative to HCs, suggesting impact of MS pathology on brain and skull development[93].

Kesler and colleagues[226] utilized maternal education as a proxy for CR in young survivors of acute lymphoblastic leukemia, and found this to be an effective predictor of cognitive outcome, improving models over medical and/or demographic predictors. Higher maternal education was associated with lower global white matter volumes in survivors after controlling for cognitive

function, suggesting that higher CR allows for greater loss of white matter before cognitive effects are manifest.

Maternal education was used as a proxy for CR given strong correlations observed between maternal education level and cognitive outcome in children[227-230]. This relationship is believed to stem from several factors, including the strong relationship between education level and intellectual functioning[231], the high correlation between parent and child IQ[232, 233], and the association between maternal education, socioeconomic status and home environment[234, 235]. Parents with higher levels of education typically have higher expectations for their child's educational attainment, as well as greater opportunities to provide their children with learning-related activities, which in turn have been linked to cognitive outcomes[236, 237]. Moreover, it is possible that higher parental education is associated with greater access to or uptake of remedial resources post-injury[238]. Parental education is thus a unique proxy for reserve, capturing a combination of heritable and environmental enrichment factors that contribute to brain and cognitive reserves in youth.

Cognitive reserve in POMS. Investigations of CR in POMS are preceded by observations of differential clinical trajectories according to age of MS onset. As previously described, individuals with POMS take, on average, 10 years longer to convert to a secondary progressive stage than adults with MS[84], though this stage is reached at a younger age[91]. This slower rate of disability accrual may reflect a higher capacity for compensatory or regenerative mechanisms in younger individuals with MS, as evidenced by a lower likelihood for T2 lesions to convert to permanent T1 black holes[90, 92]. Conversely, the onset of SPMS at a younger age may reflect earlier exhaustion of reserves, which may follow from disruptions to the development of reserves in childhood and adolescence.

Research examining the utility of CR for predicting cognitive outcomes in POMS is still in its infancy. Cross-sectionally, higher parental education has been associated with better spatial memory performance and reduced risk of cognitive impairment in POMS, but not with measures of processing speed, expressive language, or global cognition[113, 121]. In a study examining changes in cognition over one year, Till and colleagues[95] found that patients with higher educated parents were more likely to show stable or improving cognitive performance, after controlling for age at testing, age at onset, disease duration, sex, change in mood-related symptoms, IQ at first assessment, and EDSS scores. Wallach and colleagues[129] found a relationship between maternal education and risk for impairment on the SDMT at first assessment, however, maternal education was not predictive of clinically meaningful decline over 2 years. Similarly, no effect was observed for parental education on risk for decline on one or more tasks over an average of 1.6 years by

Charvet and colleagues[114], and Hosseini and colleagues found that social status (a composite measure of parental education and occupation) was not predictive of trajectories of development for working memory and processing speed[127].

More recently, Pasto and colleagues[224] found that higher CR – as measured by IQ at first assessment – was predictive of stable/improving neurocognitive performance in POMS patients over a 5-year period. Akbar and colleagues[128] also found that higher IQ at first assessment was predictive of a more positive trajectory of change in processing speed for POMS patients over time; however, no effects were observed in this study for parental education, occupation, or social status. Higher premorbid IQ (estimated by word knowledge) was also associated with reduced risk for cognitive impairment and higher occupational complexity in adults with POMS[132].

Associations between proxies for CR and cognitive outcome may be mediated by compensatory recruitment of task-related networks in POMS, as shown in fMRI studies of cognitively-preserved patients with POMS[239, 240]. Moreover, aspects of lifestyle tied to CR may serve to protect against the accumulation of MS pathology. In line with brain maintenance theory, POMS participants reporting higher physical activity show lower T2 lesion volumes, reduced relapse rates[241], and larger whole-brain grey and white matter volumes[242]. Further research is needed to expand on the existing findings, with appropriate estimations of reserve, MRI assessment of MS pathology, and comparison to HC groups.

Chapter 2: Aims & Hypotheses

The current study was conducted in coordination with the Canadian Pediatric Demyelinating Disease Study (CPDDS), and interdisciplinary and multi-site initiative spanning 23 sites in Canada and the Children's Hospital of Philadelphia. From a strength-based perspective, the overall objective of this program of research was to better understand processes facilitating protection against the cognitive presentation of neuropathology in POMS, with a specific focus on CR and its domain-specificity. Areas of deficit in POMS were first clarified, with delineation of dysfunction in speed and accuracy across neurocognitive domains.

Our first aim was to examine neuropsychological function in youth with POMS on the Penn Computerized Neurocognitive Battery (PCNB) relative to healthy age-matched controls. This is a comprehensive assessment tool not yet administered in POMS, which facilitates efficient measurement across a breadth of domains of function commonly affected in POMS, with separate measurement of accuracy and response time.

Given the proclivity of MS for white matter injury, particular attention has been given to slowed information processing, which is among the most robust cognitive findings in youth and adults with MS. Of note, information processing speed is implicated in the effective functioning of other cognitive domains and appears to contribute to a range of cognitive outcomes in adults with MS[243]. This has led to the proposition of the *Relative Consequences Model*, which posits that slowed information processing represents a fundamental deficit in MS, that in turn leads to other areas of dysfunction[137]. Following from this, the SDMT has been proposed to be an effective screener for cognitive dysfunction in MS[111, 244].

Corresponding research has not yet been conducted to examine the role of processing speed in the cognitive profile of POMS. While deficits in processing speed have been similarly robust in youth with POMS[245], we propose that these youth may have greater vulnerability to experience cognitive dysfunction in domains that are distinct from slowed information processing speed. According to the Neural Noise Hypothesis, it has been suggested that slowed processing speed corresponds to increased signal-to-noise ratio in the brain resulting from reduced efficiency and/or disruption of networks[269]. While this increased noise would contribute to dysfunction in other areas of function concurrently, such as by the *Limited Time Mechanism*[136], we anticipate that it would additionally impact the healthy development of other areas of cognitive function in POMS. Moreover, youth with POMS may demonstrate cognitive deficits which are independent from slowed processing speed due to injury to functionally-specific areas of the grey matter.

These investigations are facilitated by the development of computerized neurocognitive batteries, such as the PCNB, which enable efficient measurement of accuracy and response time concurrently across domains of cognitive assessment. Importantly, the presence of a breadth of cognitive deficits existing independently of slowed information processing points to the need for more comprehensive screening to ensure that youth experiencing cognitive challenges are effectively identified and supported.

Aim 1a: To characterize the profile of cognitive deficits in youth and young adults with POMS relative to healthy peers, and separating deficits in accuracy and response time.

Hypothesis: MS patients will show poorer performance relative to controls on PCNB tasks of processing speed, executive function (working memory, inhibition), episodic memory (verbal, visual), and complex cognition (verbal, fluid, visuospatial). Due to the onset of MS during periods of active brain and cognitive maturation, accuracy deficits across these domains were anticipated to exist over and above slowed response time.

Aim 1b: To examine cognitive impairment as classified on the PCNB relative to the SDMT, an established measure of processing speed in POMS and proposed screener for cognitive dysfunction in POMS.

Hypothesis: The PCNB will identify a broader subset of POMS patients with cognitive impairment relative to the SDMT, due to the inclusion of more diverse areas of cognitive dysfunction and presence of deficits which are distinct from slowed information processing.

While clinical and structural MRI variables of MS severity have shown some efficacy in predicting which patients will show poorer cognitive outcomes, these associations are typically modest, and a majority of youth do not show cognitive impairment until several years into the disease course[122, 245]. The theory of CR posits that people will vary in their clinical expression of neuropathology due to individual differences in capacity to adapt to brain injury[168]. CR effects have been well-established in adults with MS, using several proxies for reserve, and with evidence for moderation of the relationship between MS neuropathology and cognitive outcomes. While these effects have been shown across a range of cognitive functions, CR effects appear to have some domain specificity, with stronger associations observed for tasks of working memory and verbal learning/memory, relative to simple information processing speed[188].

Preliminary findings in POMS are mixed, and are limited in their measures for CR, as well as in the breadth of cognitive domains assessed. CR may differ in a developmental context due to the impact of early neuropathology on the development of reserves, and warrants further investigation

to inform on targets and potential mechanisms for preservation of function and/or rehabilitation for youth with POMS. We wish to expand on prior work with POMS, using parental education as a proxy for reserve and examining the domain-specificity of CR effects across the profile of cognitive dysfunction identified in Aim 1, with comparison to a HC group.

Aim 2: To examine the association between CR and cognitive function across the profile of cognitive deficits observed in Aim 1 in POMS patients relative to controls.

Hypothesis: CR will moderate the expression of cognitive deficits in youth with POMS. Youth with POMS and lower CR will demonstrate greater impairment than patients with a higher CR. Although CR may relate to cognitive performance in HCs, this relationship will be stronger in MS patients (see Figure 1). These associations are anticipated for a range of higher-level cognitive outcomes (i.e., executive functions, reasoning ability, memory, social cognition), and to a lesser extent for information processing speed.

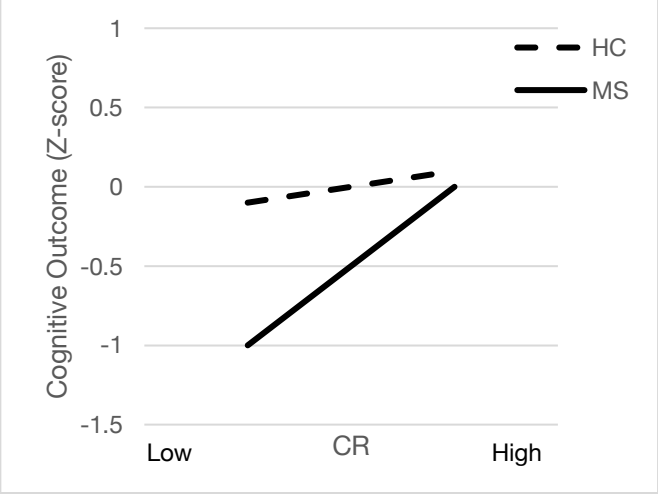

Figure 1. Anticipated findings for Aim 2: patients with high CR will not show deficit relative to controls, whereas patients with low CR will differ from controls.

Chapter 3: Examining cognitive speed and accuracy dysfunction in youth and young adults with pediatric-onset multiple sclerosis using a computerized neurocognitive battery

3.1 Publication status and author contributions

The following chapter is based on the manuscript: Barlow-Krelina, E., Fabri, T., O'Mahony, J., Gur, R. C., Gur, R. E., De Somma, E., Bolongaita, L., Dunn, C., Bacchus, M., Yeh, E. A., Marrie, R. A., Bar-Or, A., Banwell, B., & Till, C. (2021). Examining cognitive speed and accuracy dysfunction in pediatric-onset multiple sclerosis with a computerized neurocognitive battery. *Neuropsychology, 35*(4), doi: 10.1037/neu0000729

This manuscript does not exactly replicate the final version published in Neuropsychology. It is not a copy of the original published article and is not suitable for citation. Emily Barlow-Krelina, the first author, developed the conceptual rationale for the study, collected, analyzed and interpreted the data. She was also the primary contributing author to the manuscript, producing the initial draft and completing all major revisions.

3.2 Abstract

Objective. We evaluated performance on the Penn Computerized Neurocognitive Battery (PCNB), a tool assessing accuracy and response time across four cognitive domains, alongside the Symbol Digit Modalities Test (SDMT), a measure of processing speed commonly used in MS. We determined whether deficits in accuracy are observed independently of slowed information processing speed, and vice versa, in pediatric-onset multiple sclerosis (POMS).

Methods. Performance on the SDMT, accuracy on PCNB tests belonging to four domains (executive function, episodic memory, complex cognition, social cognition), and response time on the PCNB were compared for 65 POMS patients (age range: 8-29 years) and 76 healthy controls (HCs) by ANCOVA. Associations between the Overall PCNB score and SDMT were examined for both groups, and their agreement in classifying impairment was assessed using Cohen's kappa.

Results. POMS patients (age at testing=18.3±4.0 years; age at POMS onset=14.9±2.3 years) demonstrated reduced accuracy relative to HCs on tests of working memory, attention/inhibition, verbal memory and visuospatial processing, after adjusting for response time ($p \leq .002$). Patients demonstrated slower overall response time on the PCNB ($p=.003$), while group differences on the SDMT did not meet significance ($p=.03$). Performance on the PCNB and SDMT were correlated (MS: $r=0.43$, HC: $r=0.50$, both $p<.001$), however, the degree of agreement for impairment was minimal ($k=0.22$, $p=.14$).

Conclusion. Specific cognitive deficits exist independently of slowed information processing speed in POMS and may represent more significant areas of dysfunction. Delineation of accuracy and response time in neuropsychological assessment is important to identify areas of cognitive deficit in POMS.

3.3 Introduction

Cognitive impairment occurs in approximately 30% of youth and young adults with pediatric-onset multiple sclerosis (POMS), with deficits observed in processing speed, executive function, memory, language, fluid reasoning, visuospatial ability, and visuomotor integration[97, 102, 124, 165, 246-248]. Among these, slowed information processing is one of the most robust cognitive findings, leading to use of the Symbol Digit Modalities Test (SDMT) as a screening tool for cognitive impairment[111]. Slowed processing speed is believed to arise as a consequence of the widespread loss of integrity of white matter pathways[134]. Indeed, slowed performance on the SDMT has been strongly associated with structural MRI measures that reflect widespread white matter injury, including smaller thalamic volume and lower fractional anisotropy values in hemispheric, corpus callosum, and thalamic regions in POMS[97, 102, 135].

Importantly, slowed information processing can interfere with the learning of new information, and with tasks requiring greater cognitive demand[136]. In fact, it has been proposed that slowed processing speed may represent the primary deficit in MS, which in turn leads to inefficiencies – and ultimately deficits – in a range of other cognitive functions [137]. This theory is termed the *Relative Consequences Model*, and has been supported by studies showing that processing speed contributes significantly to variance in performance on tasks of executive function, social cognition and memory in adults with MS[138-146]. The role of processing speed has been less studied in the cognitive profile of POMS. This relationship may differ in the context of developing cognitive function, with some deficits appearing to exist independently of slowed information processing[125].

In recent years, there has been a growing interest in computerized tools for neuropsychological assessment, which offer efficient and standardized measurement of cognitive function on an interface that is user-friendly for children and adolescents[249]. Importantly, these tools facilitate the measurement of both accuracy and response time, allowing for delineation between performance that is impaired as a result of, or independently from slowed information processing.

The Penn Computerized Neurocognitive Battery (PCNB;[147] is one such tool that takes approximately one hour to complete. Similar to more comprehensive paper-and-pencil neuropsychological batteries recommended for MS and POMS[115, 244], the PCNB evaluates executive functions, episodic memory, verbal reasoning, visuospatial processing and sensorimotor speed. The battery also includes measures of social cognition and fluid reasoning. The PCNB has shown good internal consistency, as well as a factor structure consistent with domains of Executive Function, Complex Cognition, Social Cognition and Memory[148, 250]. The PCNB was developed

to measure neurocognitive function using tests previously validated with functional neuroimaging[149], and has shown expected sex differences and change in cognitive performance with age in a sample of 3500 youth and young adults[147]. The PCNB has also been applied to diverse clinical populations, effectively differentiating neurocognitive profiles between controls and people with chronic kidney disease, 22q11.2 deletion syndrome, mood disorders, and exposures to herpes simplex virus or hepatitis C[151-155]. With separate measures for accuracy and response time that are available across a breadth of cognitive domains, the PCNB may offer new insights on the neurocognitive profile of POMS.

We used the PCNB to measure neurocognitive functioning in youth and young adults with POMS relative to age-matched controls. To distinguish poor performance in specific cognitive domains from slowed processing speed, accuracy of performance was evaluated with adjustment for task-specific response time, and vice versa. Performance on the PCNB was evaluated alongside the SDMT to allow for comparison to an established measure of processing speed impairment in POMS. We examined the association between performance on the PCNB and the SDMT, and assessed the consistency between these two measures in classifying impairment. Finally, on tasks where POMS patients demonstrated deficits relative to controls, we examined associations between task performance and clinical predictor variables (including age at disease onset, disease duration, neurological disability, fatigue and emotional distress).

3.4 Method

Participants. Between September 2004 and August 2015, youth with acquired demyelinating syndromes under age 16 years and within 90 days of disease onset were enrolled in the Canadian Pediatric Demyelinating Disease Study (CPDDS). The CPDDS includes 23 sites across Canada and the Children's Hospital of Philadelphia. Participants were classified as having POMS per the 2017 McDonald Diagnostic Criteria [49], monophasic demyelination, relapsing demyelination not consistent with MS, or diagnosis other than demyelination. Inclusion criteria were modified between August 2015 and June 2019 such that only youth aged less than 18 years who consented within 180 days of disease onset and met the 2017 McDonald Diagnostic Criteria [49] were enrolled. Patients with monophasic demyelination, those identified as having MOG-related demyelination, anti-AQP4-related neuromyelitis optica spectrum disorder, or non-demyelinating disease were excluded from the present analysis.

Between December 2015 and June 2019, all English-speaking participants involved in the CPDDS were offered participation in neurocognitive testing. Healthy control participants (HCs) were also enrolled at this time using flyers and web-based advertising.

Research ethics approval was obtained by all participating institutions. Written informed consent was obtained from participants or a parent/legal guardian.

Measures. We used standardized case report forms to record demographics, developmental milestones and medical histories (including date of MS onset, disease duration from first attack, and the type and duration of treatment with disease-modifying therapies). Study site neurologists documented neurological findings as described previously, leading to determination of an approximated Expanded Disability Status Scale score (EDSS;[57, 89]. We measured symptoms of depression and anxiety using the Pediatric Index of Emotional Distress (PI-ED;[251] and the Hospital Anxiety and Depression Scale (HADS[252] for participants below and at/above 16 years of age, respectively. For each of these measures, scores range from 0-42; a score greater than 20 is indicative of clinically significant emotional distress. We measured self- and parent-reported fatigue using the PedsQL Multidimensional Fatigue Scale; scores range from 0-100, with higher scores reflecting fewer problems[253]. Social status was measured by the Barratt Simplified Measure of Social Status (BSMSS), which yields a score between 8-66[254]. Participants also reported the number of years of education completed by themselves and each of their parents; these values were averaged to give a numerical value for parental education.

Cognitive Evaluation. Participants completed the oral version of the SDMT[255] and the PCNB[256]. The PCNB assesses: executive function (i.e., abstraction and cognitive flexibility, working memory, attention and inhibition), episodic memory (i.e., face, object, word), complex cognition (i.e., language, nonverbal reasoning, spatial processing), social cognition (i.e., emotion identification, emotion and age differentiation), and sensorimotor speed (i.e., finger tapping speed, motor praxis). Each test on the PCNB provides a measure of both accuracy and response time, with the exception of sensorimotor tests designed for assessing speed. These tests are described in Table 1.

All assessors completed a standard training protocol for PCNB administration[147]. The battery was administered in a single session of approximately one hour, with breaks offered at three standard intervals. To ensure understanding of task instructions, practice trials were administered ahead of each task (with the exception of the Penn Conditional Exclusion Task). During neurocognitive testing, the assessor documented behavioral and environmental observations pertinent to testing (e.g., distractions, motivation, misunderstanding of instructions). The data underwent quality control procedures, including identification of outliers for response time and multiple key-presses[147]. Assessor comments were examined and invalid participant data were excluded.

To derive age-normed scores for the PCNB that were appropriate to our predominantly Canadian sample, we standardized raw scores for each outcome into *Z*-scores based on the means and standard deviations (SD) of the HCs. *Z*-scores were calculated from four age bands (i.e., 8-10, 11-13; 14-17; ≥18 years) that were determined based on the developmental curves for each test[147] and with consideration of the number of participants in each group (n = 10, 12, 40 and 32, respectively). Response time scores were transformed so that higher *Z*-scores would reflect better performance (i.e., shorter response times). For consistency, we used data from our HC group to derive *Z*-scores for the SDMT by the same method used for the PCNB; however, scores derived from the published American norms for the oral SDMT (Smith, 1982) are also reported in our supplemental table for better comparison to existing studies. We did not derive *Z*-scores using the Philadelphia-based normative PCNB dataset as they were deemed non-representative of the demographics of our primarily Canadian study sample[147], leading to positively skewed *Z*-scores for both groups.

Composite domain scores were computed for accuracy according to the established factors for the PCNB: Executive Function, Episodic Memory, Complex Cognition and Social Cognition[148]; confirmatory factor analysis supported this factor structure for the youth and young adults with MS and HCs included in this study (data not shown). These scores were created by averaging accuracy *Z*-scores on each test within each of the four domains. Response time was averaged across tests belonging to three previously established factors (i.e., time-constrained, open-window, memory;[148]. These factor scores were averaged to create an overall domain score for Response Time. Scores on the five domains served as the main outcomes along with an Overall PCNB score (i.e., an average of the 12 accuracy and three response time outcomes). The response time factors, domain scores, and Overall PCNB score are outlined with their respective subtests in Table 1.

Participants were deemed impaired on a test if their *Z*-score fell ≥ 1.5 SD below the mean. Cognitive impairment was defined as impaired performance on four or more of the 15 PCNB outcomes included in the Overall PCNB score. Based on studies of healthy, typically-developing individuals, the probability of exceeding this cutoff criterion by chance is estimated to be less than 7%[257].

Table 1. Description of neurocognitive tasks and composite scores derived from the Penn Computerized Neurocognitive Battery

Domain	Subtests	Neurobehavioural function	Brief Test Description
Executive Function[a]	Short Letter N-Back	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
	Penn Conditional Exclusion Test	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 Task	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
Episodic Memory[a]	Penn Face Memory Test	face recognition memory	identify which faces have been seen previously
	Penn Word Memory Test for Children	verbal recognition memory	identify which words have been seen previously
	Short Visual Object Learning Test	spatial recognition memory	identify which figures have been seen previously
Complex Cognition[a]	Short Penn Verbal Reasoning Test for Children	verbal reasoning	select from a list the word that best completes the verbal analogy
	Penn Matrix Analysis Test	nonverbal reasoning	choose the geometric piece that best completes the pattern
	Variable Short Penn Line Orientation Test	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
Social Cognition[a]	Age Differentiation Task	age differentiation, visual discrimination	identify which of two faces is older
	Penn Emotion Recognition Test for Children	emotion identification	identify the emotion shown on a given face from a list of emotions
	Measured Emotion Differentiation Task	emotion differentiation	identify which of two faces is showing an emotion to a greater degree

Factor	Subtests	Neurobehavioural function	Brief Test Description
Time-Constrained RT[b]	Short Letter N-Back	speeded responding within a fixed response window	
	Go-No-Go Task		
	Motor Praxis Test		quickly manipulate a computer mouse to click on a target that moves and changes size
	Short Penn Computerized Finger-Tapping Test		tap the spacebar using only the index finger as many times as possible within 10 000ms
Open-window RT[b]	Penn Conditional Exclusion Test	time taken to respond when provided with an open-ended response window	
	Short Penn Verbal Reasoning Test for Children		
	Penn Matrix Analysis Test		
	Variable Short Penn Line Orientation Test		
	Age Differentiation Task		
	Penn Emotion Recognition Test for Children		
	Measured Emotion Differentiation Task		
Memory RT[b]	Penn Face Memory Test	speed of retrieval for tests of recognition memory	
	Penn Word Memory Test for Children		
	Short Visual Object Learning Test		
Composite	**Subtests/Factors**	**Neurobehavioural function**	
Response Time	Time-constrained RT	global response time	
	Open-window RT		
	Memory RT		

Overall PCNB	Short Letter N-Back[a]	global cognitive function
	Penn Conditional Exclusion Test[a]	
	Go-No-Go Task[a]	
	Penn Face Memory Test[a]	
	Penn Word Memory Test for Children[a]	
	Short Visual Object Learning Test[a]	
	Short Penn Verbal Reasoning Test for Children[a]	
	Penn Matrix Analysis Test[a]	
	Variable Short Penn Line Orientation Test[a]	
	Age Differentiation Task[a]	
	Penn Emotion Recognition Test for Children[a]	
	Measured Emotion Differentiation Task[a]	
	Time-constrained RT	
	Open-window RT	
	Memory RT	

Test	**Neurobehavioural function**	**Brief Test Description**
Symbol Digit Modalities Test	information processing speed	quickly name the numbers that correspond to symbols listed on a page, according to a key, within 90s

Abbreviations: RT = response time; PCNB = Penn Computerized Neurocognitive Battery

a – accuracy scores

b – response time scores

Data Analysis. We used one-way analysis of variance (ANOVAs) or chi-squared (X^2) tests to compare the POMS and HC groups on demographic variables, as well as on the fatigue and emotional distress scores. For all PCNB scores, outliers were Winsorized to 3 SD from the mean. Statistical significance was established using an adjusted *p*-value of < .01 *(two-tailed)* to guard against a false positive. Analyses were performed using IBM SPSS Statistics version 24 (Armonk, NY: *IBM* Corp), with the exception of the partial Spearman correlations, which were conducted on R Studio AGPL v3, using package RVAideMemoire.

Main Outcomes. Univariate ANCOVAs were run to compare groups on each cognitive domain, adjusting for sex and demographic variables that differed significantly between groups at *p* < .10 (i.e., parental education). The response times for tasks corresponding to each domain were averaged and included as a covariate for analyses of accuracy on each domain. Similarly, for analyses of response time factors, accuracy on the corresponding tests were averaged and included as a covariate. Univariate ANCOVAs were also run for the Overall PCNB score and the SDMT. Effect sizes were determined using Cohen's *d*. Interactions between our covariates (accuracy, response time) and group were examined to test for homogeneity of regression slopes, as well as to assess the contribution of these covariates to group differences in the cognitive outcomes.

Supplemental Outcomes. Where there were significant differences by group for PCNB domains, univariate ANCOVAs were run to examine group differences at the test- or response time factor-level. These test-level comparisons were also run for raw scores, controlling for age, to confirm that the pattern of group differences was robust to our method of score standardization.

Overall cognitive impairment on the PCNB and SDMT was compared between groups using adjusted binary logistic regression. Rates of impairment were also compared between groups for PCNB subtests where POMS patients demonstrated significantly poorer performance than HCs. Sex, task-specific response time/accuracy and parental education were included as covariates for each of these models.

Cohen's kappa was obtained to examine the consistency between impairment classification between the PCNB and SDMT. Pearson correlations were also conducted to examine the relationship between the Overall PCNB score and SDMT for each group separately.

Finally, partial Spearman correlations were used to examine associations between the profile of cognitive deficits and clinical predictor variables (i.e., age at disease onset, disease duration, EDSS, symptoms of emotional distress, self and parent-reported fatigue). We controlled for response time when examining the association between clinical variables and PCNB task performance, and vice versa. We also controlled for age at disease onset when looking at

relationships between disease duration and task performance, and vice versa.

3.5 Results

Of the 80 POMS patients and 139 HCs in the CPDDS who were eligible to complete the PCNB, neurocognitive data were obtained for 67 (83.7%) POMS patients from nine study sites (51 from Toronto and Philadelphia) and 95 (68.3%) HCs (all from Toronto and Philadelphia; see Figure 2). Thirteen POMS patients declined completion of the PCNB; POMS participants who completed neurocognitive testing had a later age at onset compared to those who declined, but did not differ on any other demographic features. We excluded data for one patient due to significant visual/motor impairment, one patient due to potential impact of intravenous therapy occurring concurrently with testing on response times, and one HC due to their expressed familiarity with the assessment battery. Among the 94 HCs with valid data on the PCNB, we excluded 18 participants who were 13 years and younger to enhance the age-matching between the groups. The retained HCs were selected at random, after matching to the four MS participants in the 8-13 age range, based on their age and sex.

The final sample of 65 POMS and 76 HCs did not differ with respect to age, sex, level of education, socioeconomic status or emotional distress. POMS patients reported significantly higher self- and parent-reported fatigue relative to HCs (p values < .01), as well as a trend towards lower parental education (p = .06). Clinical and demographic characteristics of the sample are described in Table 2.

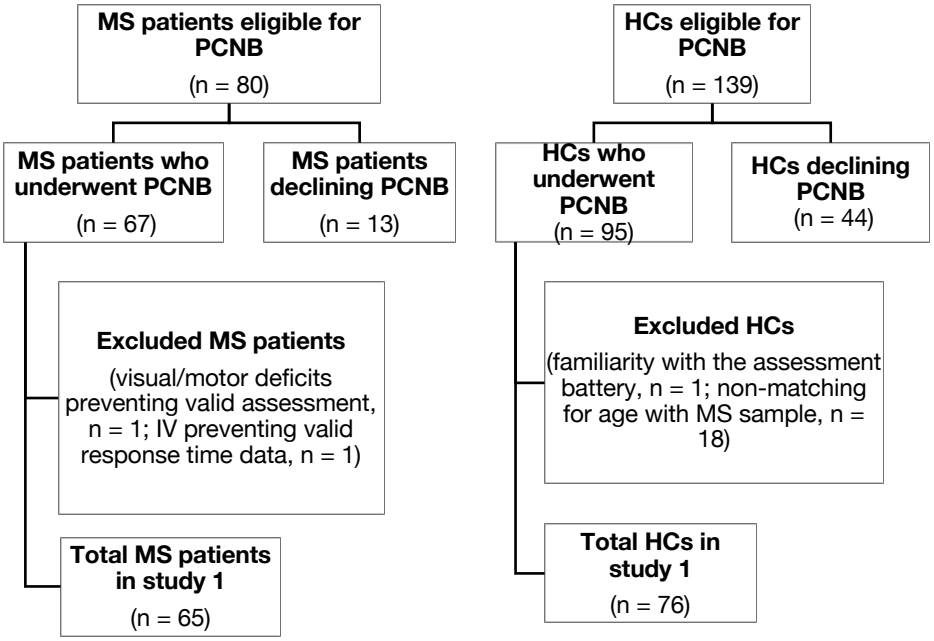

Figure 2. Patient enrollment from the Canadian Pediatric Demyelinating Disease Study for Study 1.

Table 2. Demographic and clinical characteristics of pediatric-onset MS and healthy control participants in Study 1

	MS (n=65) M(SD) / N (%)	**HC (n=76)** M(SD) / N(%)	***p***	**Cohen's *d***
Age at testing (years)	18.3 ± 4.0 (8-27)	18.1 ± 4.6 (8-29)	.87	0.03
Sex (#female, %female)	48 (73.8)	49 (64.5)	.28	
Participant education (years)	11.7 ± 3.1 (2-19)	12.1 (3-20)	.53	0.11
Parental education	14.3 ± 1.9 (10-19)	15.0 ± 2.3 (10-20)	.06	0.33
Socioeconomic status	39.6 ±14.6 (8.5-66)	43.1 ± 14.4 (10-66)	.16	0.25
Nationality (#Canadian, %Canadian)	48 (73.8)	58 (76.3)	.85	
Emotional Distress† (#high, %high)†	6 (10.0)	3 (5.0)	.49	
Participant Fatigue				
Parent-rated	69.9 ± 20.8 (33.3-100)	84.1 ± 14.8 (45.8-100)	**<.001**	0.78
Participant-rated	64.5 ± 20.9 (26.4-98.6)	74.3 ± 14.3 (43.1-100)	**.002**	0.55
Age at disease onset (years)	14.9 ± 2.3 (6.3-17.9)	-	-	
Disease Duration (months)	45.3 ± 45.8 (0-133)	-	-	
EDSS (median, range)	1.5 (0-6.5)	-	-	
DMT (#Y, %yes)	53 (81.5)	-	-	
DMT duration† (months; median, range)	34 (0-123)	-	-	

Abbreviations: MS = multiple sclerosis; HC = healthy control; EDSS = Expanded Disability Status Scale; DMT = Disease Modifying Therapy

Note. Parental education data was not available for 4 MS and 2 HCs. Social status data was not available for 4 MS patients and 7 controls. Emotional distress data was not available for 5 POMS patients and 15 controls. Parent-rated fatigue data was not available for 11 patients and 24 controls. Participant-rated fatigue data was not available for 3 patients and 7 controls.

Neurocognitive Outcomes. Performance on the Overall PCNB score was lower for participants with POMS relative to the HC group (Mean *Z*-score = -0.34 vs. -0.01, Cohen's *d* = 0.73, *p* < .001). Accuracy scores were lower for POMS patients relative to HCs on three of the four PCNB domains (adjusting for response time, sex and parental education): Executive Function, Episodic Memory and Complex Cognition, but not Social Cognition (Table 3). POMS patients also demonstrated slower overall Response Time on the PCNB relative to HCs (Mean *Z*-score = -0.24 vs. 0.05, Cohen's *d* = 0.55, *p* = .003).

Task-specific group differences were found on the following: Letter N-Back (Mean *Z*-score = -0.89 vs. -0.04, Cohen's *d* = 0.66, *p* < .001), Go-No-Go (Mean *Z*-score = -0.79 vs. -0.01, Cohen's *d* = 0.56, *p* = .002), Verbal Memory (Mean *Z*-score = -0.63 vs. -0.03, Cohen's *d* = 0.56, *p* = .002), and Line Orientation tasks (Mean *Z*-score = -0.69 vs. -0.02, Cohen's *d* = 0.59, *p* = .001). No significant group differences were found for the specific PCNB response time factors, nor on the SDMT (Table 3). Group comparison of raw scores and SDMT Z-scores derived from the published norms revealed a similar pattern of findings; significant differences were observed between groups on the Letter N-Back, Go-No-Go, Verbal Memory and Line Orientation subtests (Supplemental Table 1). No significant group x response time interactions were found for analyses of accuracy, nor were there any significant group x accuracy interactions found in analyses of response time (the contribution of these covariates to group differences in cognitive outcomes are illustrated in Supplemental Table 2).

Nineteen of 65 (29.2%) POMS patients met criteria for overall cognitive impairment (i.e., at least four of 15 tests with a *Z*-score ≥1.5 SD below the mean), compared with six of 76 (7.9%) HCs (*OR* = 3.68, 95% CI: 1.32, 10.31, *p* = .01). On the SDMT, 10 of 58 (17.2%) POMS patients compared with 3 of 60 (5.0%) HCs had impaired performance (*OR* = 2.94, 95% CI: 0.73, 11.76, *p* = .13). Rates of impairment were higher for POMS participants relative to HCs on the Letter N-Back (*OR* = 3.68, 95% CI: 1.45, 9.35, *p* = .006), Go-No-Go (*OR* = 4.02, 95% CI: 1.41, 11.36, *p* = .009) and Line Orientation tasks (*OR* = 5.52, 95% CI: 1.66, 18.52, *p* = .005; Table 3).

Table 3. Estimated marginal means of composite scores and subtest Z-scores, and the number of participants in each group demonstrating impaired performance on the Penn Computerized Neurocognitive Battery and the Symbol Digit Modalities Test

Domain	Test	MS		HC		Group difference		Proportional analysis
		M(SE)	*Impaired % (n/N)*	*M(SE)*	*Impaired % (n/N)*	*p*	*Cohen's d*	*p*
Executive Function[a]		-0.57 (0.11)		-0.04 (0.10)		**0.001**	0.62	
	Letter N-Back	-0.89 (0.17)	35.5 (22/62)	-0.04 (0.15)	10.8 (8/74)	**< 0.001**	0.66	**0.006**
	PCET	-0.13 (0.14)		-0.06 (0.13)		0.70	0.06	
	Go-No-Go	-0.79 (0.18)	26.2 (17/65)	-0.01 (0.16)	7.9 (6/76)	**0.002**	0.56	**0.009**
Episodic Memory[a]		-0.45 (0.10)		0.00 (0.09)		**0.001**	0.58	
	Face Memory	-0.30 (0.13)		-0.01 (0.12)		0.11	0.28	
	Spatial Memory	-0.33 (0.15)		-0.02 (0.13)		0.12	0.27	
	Verbal Memory	-0.63 (0.14)	23.0 (15/65)	-0.03 (0.12)	11.8 (9/76)	**0.002**	0.56	0.15
Complex Cognition		-0.46 (0.11)		-0.01 (0.09)		**0.002**	0.58	
	Verbal Reasoning	-0.46 (0.16)		-0.01 (0.16)		0.04	0.35	
	Matrix Reasoning	-0.22 (0.08)		-0.02 (0.07)		0.06	0.33	
	Line Orientation	-0.69 (0.15)	26.2 (17/65)	-0.02 (0.13)	5.3 (4/75)	**0.001**	0.59	**0.005**
Social Cognition[a]		0.01 (0.09)		-0.02 (0.08)		0.87	-0.04	
Response Time		-0.24 (0.07)		0.05 (0.06)		**0.003**	0.55	
	Time-constrained	-0.14 (0.09)		0.04 (0.08)		0.14	0.26	
	Open-window	-0.14 (0.08)		0.04 (0.07)		0.10	0.29	
	Memory	-0.34 (0.12)		-0.01 (0.11)		0.05	0.35	
Overall PCNB		-0.34 (0.06)	29.2 (19/65)	-0.01 (0.05)	7.9 (6/76)	**< 0.001**	0.73	**0.01**

SDMT	-0.40 (0.14)	17.2 (10/58)	0.02 (0.13)	5.0 (3/60)	0.03	0.41	0.13

Abbreviations: MS = multiple sclerosis; HC = healthy control; PCET = Penn Conditional Exclusion Test; PCNB = Penn Computerized Neurocognitive Battery; SDMT = Symbol Digit Modalities Test

a – accuracy scores

Note. P-values represent group differences after adjusting for response time/accuracy, parental education and sex using ANCOVA or logistic regression. Classification of impairment was based on a score falling 1.5 standard deviations below the mean. For the overall PCNB score, participants were classified as impaired if 4 or more of the 15 outcomes (12 cognitive tests and 3 RT measures) were below 1.5 standard deviations from the mean. Cohen's *d*'s of 0.2, 0.5, and 0.8 reflect small, medium and large effect sizes. Sample size differs across tests due to exclusion of invalid data.

Comparison between the PCNB and SDMT. Performance on the Overall PCNB score was positively associated with performance on the SDMT for both POMS patients (r = 0.43, 95% CI: 0.19, 0.62, $p < .001$) and HCs (r = 0.50, 95% CI: 0.28, 0.67, $p < .001$); however, the degree of agreement between the PCNB and SDMT for classification of impairment in POMS patients was weak (k = 0.22, p = .14). Of the 16 POMS patients who completed both SDMT and PCNB testing and demonstrated impairment on the PCNB, only five (31.3%) showed impaired performance on the SDMT. Of the 10 POMS patients demonstrating impairment on the SDMT, five (50.0%) were impaired on the PCNB.

Associations to clinical variables. A longer disease duration was associated with poorer accuracy on the Line Orientation (*rho* = -0.32, 95%CI: -0.53, -0.03, $p < .001$) and Verbal Memory tasks (*rho* = -0.19, 95%CI: -0.42, 0.09, p = .01), after adjusting for age at onset and task-specific response time. No other significant associations were observed between clinical variables and performance on tasks where POMS patients demonstrated deficits relative to HCs. Associations were not examined for the EDSS, given the restricted range of scores for the majority of participants (89.2% with scores spanning 0-2).

3.6 Discussion

We examined neurocognitive functioning in POMS patients using the PCNB, a computerized battery that evaluates neurocognitive performance in accuracy and response time. Approximately 29% of patients were classified as cognitively impaired based on their performance on the PCNB. POMS participants had lower accuracy on tests of executive function, episodic memory and complex cognition compared to HCs, as well as slower overall response times on the PCNB. The rate of cognitive impairment and profile of deficits in our sample was generally consistent with prior studies examining neurocognitive function in POMS[124, 165, 246, 247], thus providing evidence for the validity of PCNB in detecting neurocognitive dysfunction in POMS; however, the PCNB facilitated additional differentiation of deficits in accuracy and response time.

Large effects for reduced accuracy were found in several cognitive domains even after adjusting for slowed response time, and variance in response time did not contribute significantly to these group differences. Although slowed information processing may still impact these aspects of cognitive function, our findings conflict with the hypothesis that slowed information processing represents a *foundational* deficit underlying other areas of dysfunction in MS. While greater evidence exists in support of this theory in adults with MS[137], we anticipated that the role of processing speed might differ in the neurocognitive profile of POMS. Our findings were indicative

that some aspects of cognitive dysfunction exist independently of information processing speed in youth with MS, potentially resulting from the accrual of brain injury during formative years of cognitive development or greater differentiation of functions in younger individuals (Hülür et al., 2015).

Executive function deficits were among the most apparent in our sample, with rates of impairment reaching up to 35% in POMS patients. As previously observed using paper-and-pencil tasks of executive function, our POMS patients demonstrated poorer accuracy on tests of sustained attention/response inhibition and working memory, but not on a test of cognitive flexibility[100, 102]. Group differences on tests of executive function were apparent after adjusting for response time, suggesting that these deficits may exist over and above slowed processing speed. Importantly, these tasks were designed with fixed response intervals of up to 2.5 seconds; slowed processing speed may thus have contributed to poorer accuracy scores on these tasks, as participants may have compromised accuracy to maintain speeded responding within the response window.

Within the domain of Complex Cognition, we found that youth with POMS had reduced accuracy on a judgement of line orientation task, while performance on the matrix reasoning task remained relatively unimpaired[124, 165]. Together with the existing literature, these findings suggest greater difficulty with visuospatial tasks with higher visual-perceptual demands and relative sparing of visual problem-solving. POMS patients also demonstrated moderately lower accuracy in verbal reasoning relative to HCs, though group differences did not meet our statistical threshold[101, 102].

Examining tests of episodic memory, we found that the POMS group demonstrated reduced accuracy on a test of verbal recognition. This finding was observed after adjusting for response time, suggesting that the observed deficits are not related to the speed of recognition. It remains unclear, however, whether a slowed speed of processing could contribute to difficulties learning the words when they were initially presented at 5s intervals. Contrary to prior studies[95, 101, 112, 121], group differences were not observed on the visual memory tests. Deficits with recall, which are most commonly observed among patients with POMS[103, 120, 121, 163], cannot be ruled out as long-term memory was not assessed.

Our groups did not differ on the social cognition measures of the PCNB. In a previous study on social cognition in POMS, these youth were observed to show poorer theory of mind on both affective and cognitive tests after adjusting for processing speed[125]. The social cognition tests on the PCNB are comparatively simpler to the higher-level social cognition tests studied previously, with greater reliance on visual discrimination and less demand on theory of mind. It is possible that

we did not observe effects for social cognition due to differences in test requirements or task sensitivity. Further research is needed to replicate and elucidate the nature of social cognition deficits in POMS.

Group differences were not significant on the time-constrained, open-window, and memory response time factors on the PCNB, which are believed to correspond to Cattell-Horn-Carroll's decision speed/reaction time and processing speed, and with speed of recognition, respectively[148, 258]. A moderate effect size was, however, observed for the memory factor, suggesting that reduced speed may be more apparent for youth and young adults with POMS on tests of memory. While group effects for the time-constrained tasks were minimal, it is possible that slowed information processing speed may have had greater impact on accuracy for these tasks, as described above. Of note, POMS patients demonstrated an overall pattern of slowed responding relative to HCs when examining response time on the PCNB as a whole. This is consistent with existing evidence for slowed information processing in individuals affected by POMS, which might affect speeded performance across several of the response time factors.

Although group differences on the SDMT did not meet our statistical threshold of $p < .01$, our patients demonstrated moderately slower processing speed than controls on this task, with similar effect sizes to what has been reported previously in POMS[101, 111]. These *Z*-scores were also in a range similar to prior Canadian cohorts when using the existing American norms for POMS patients and HCs (Supplemental Table 1;[97, 102].

Overall performance on the PCNB was correlated with the SDMT for POMS patients and controls, however, the patients identified as impaired differed between these measures. One-third of participants who were classified as cognitively impaired on the PCNB were also impaired on the SDMT, while 50% of participants impaired on the SDMT were impaired on the PCNB. This incongruity is in line with the wider scope of abilities captured within the criteria for impairment on the PCNB, as compared to the more specific deficits measured using the SDMT. Exclusive use of the SDMT as a screen for cognitive impairment may thus not identify individuals presenting with difficulties outside of processing speed and visual working memory.

Examining associations to clinical variables, we found poorer cognitive performance for youth with a longer history of POMS. Similar to prior studies, this effect was most prominent for visuospatial processing[95, 110, 130], but was also found for verbal memory. Similar to prior studies, self- and parent-reported fatigue was greater in POMS patients relative to controls[165], however, the groups did not differ in their self-report of clinically significant emotional distress, with fewer patients reporting distress than expected based on the literature (approximately 30%).

Moreover, no associations were found between reported symptoms of fatigue or emotional distress and task performance where POMS participants showed cognitive deficits.

Our study has several limitations. We derived *Z*-scores based on four age bands within our HC sample of 94 participants with valid neurocognitive data. As such, our *Z*-scores have limited specificity to individuals of a particular age. While the Philadelphia Neurodevelopmental cohort of over 9000 individuals aged 8 to 21 serve as the published normative dataset for the PCNB[148], we determined that these norms could not be appropriately utilized for non-American populations (approximately 75% of our sample). Similar to existing literature[259, 260], the application of the Philadelphia-based norms led to positively skewed *Z*-scores in our MS and control sample. Importantly, our HC participants were proportionally representative of our MS participants for nationality. The data were also analyzed using raw scores (Supplemental Table 1), adjusting for age and sex, and confirmed a consistent overall pattern of findings to our analysis of standardized scores.

The pediatric version of the PCNB was used for all participants for consistency in administration, despite our assessment of participants up to the age of 28 years. Instructions and vocabulary (for verbal stimuli) are simplified in the children's version of the cognitive flexibility, verbal reasoning, verbal memory and emotion identification tests. Of note, we found that the distribution in raw scores was similar between the 14-17 and 18+ groups. Group differences were also observed where expected for these tests, suggesting that the pediatric versions were sufficiently sensitive to detect deficits.

Finally, 16.3% of the CPDDS sample meeting eligibility for the current study declined participation in neurocognitive testing. While our sample is comparable to other North American cohorts previously reported with regards clinical and demographic factors, and our results replicate patterns of neurocognitive dysfunction observed in POMS, it is possible that the current findings have limited generalizability to POMS patients as a whole.

We show that a one-hour computerized battery identified POMS patients with reduced processing speed, executive function, episodic memory and complex cognition performance relative to healthy age-matched youth. Deficits in working memory, attention/inhibition, visuospatial processing and verbal memory were observed after adjusting for task-specific response time, suggesting that these areas of dysfunction may represent core deficits that exist over and above slowed information processing speed. Supports that are specific to these aspects of cognition (e.g., seating close to the teacher, visual cueing, repetition of instructions) may thus be important to facilitate better functioning in POMS, in addition to the provision of additional time for task completion. Moreover, given the different subset of POMS patients identified as cognitively

impaired based on the PCNB versus the SDMT, it is recommended that the cognitive screening of individuals with POMS be expanded beyond simple assessment of processing speed, to include the above listed aspects of cognitive function.

Given that these same domains have shown impairment in other POMS cohorts and the overall rates of cognitive impairment were comparable to the literature, we posit that the PCNB may be valuable for measurement of cognitive dysfunction in research contexts. Research comparing the PCNB to a full neuropsychological battery is needed, however, to confirm its utility for clinical screening of cognitive impairment. Future studies should examine the role of processing speed on tasks of learning and free recall, theory of mind, and untimed tasks of executive function.

Supplemental Table 1. Comparison of groups on raw scores of the Penn Computerized Neurocognitive Battery and alternative scoring methods for the Symbol Digit Modalities Test

Domain	Test	MS	HC	Group difference	
		M(SE)	*M(SE)*	*p*	*Cohen's d*
Executive Functi	Letter N-Back	92.20 (0.91)	95.82 (0.81)	**0.004**	0.52
	PCET	2.39 (0.09)	2.43 (0.08)	0.74	0.06
	Go-No-Go	94.33 (0.55)	96.38 (0.49)	**0.005**	0.48
Episodic Memory	Face Memory	77.96 (1.30)	80.82 (1.19)	0.11	0.28
	Spatial Memory	77.43 (1.65)	80.53 (1.49)	0.17	0.24
	Verbal Memory	93.02 (0.70)	95.72 (0.63)	**0.006**	0.50
Complex Cognition	Verbal Reasoning	83.54 (1.88)	88.72 (1.64)	0.03	0.37
	Matrix Reasoning	60.87 (1.60)	64.63 (1.45)	0.09	0.30
	Line Orientation	60.65 (2.34)	69.56 (2.13)	**0.006**	0.49
Social Cognition	Age Differentiation	73.63 (1.32)	73.53 (1.20)	0.96	0.01
	Emotion Recognition	90.61 (0.82)	89.54 (0.74)	0.07	0.45
	Emotion Differentiation	75.73 (1.33)	78.08 (1.20)	0.19	0.23
SDMT[a]		61.39 (1.77)	64.89 (1.70)	0.16	0.27
SDMT[b]		0.25 (0.17)	0.76 (0.17)	0.04	0.40

Abbreviations: MS = multiple sclerosis; HC = healthy control; PCET = Penn Conditional Exclusion Test; SDMT = Symbol Digit Modalities Test

a – raw scores

b – Z-scores derived from American norms for the oral SDMT

Note. P-values represent group differences after adjusting for parental education, age and sex using ANCOVA. Task-specific response time was included as an additional covariate for the tasks on the Penn Computerized Neurocognitive Battery. Cohen's *d*'s of 0.2, 0.5, and 0.8 reflect small, medium and large effect sizes. Sample size differs across tests due to exclusion of invalid data.

Supplemental Table 2. Effect size for group difference in cognitive outcomes with and without response time/accuracy covariates

Domain	Test	Cohen's *d*	
		adjusting for RT/accuracy	without adjustment for RT/accuracy
Executive Function		0.59	0.62
	Letter N-Back	0.64	0.66
	PCET	0.06	0.06
	Go-No-Go	0.50	0.56
Episodic Memory		0.57	0.58
	Face Memory	0.31	0.28
	Spatial Memory	0.24	0.27
	Verbal Memory	0.66	0.56
Complex Cognition		0.45	0.58
	Verbal Reasoning	0.36	0.35
	Matrix Reasoning	0.13	0.33
	Line Orientation	0.52	0.59
Social Cognition		0.00	0.04
RT		0.36	0.55
	Time-constrained	0.16	0.26
	Open-window	0.23	0.29
	Memory	0.35	0.35

Abbreviations. RT = response time; PCET = Penn Conditional Exclusion Test

Chapter 4: Cognitive reserve in pediatric-onset MS: Examining parental education as a predictor of cognitive dysfunction

4.1 Publication status and author contributions.

The following chapter has been drafted as a manuscript. The contents have been reviewed by the following authors: Barlow-Krelina, E., Turner, G. R., Wojtowicz, M., Banwell, B., & Till, C. Authors Fabri, T.L., O'Mahony, J., Gur, R. C., and Gur, R. E. also contributed to this work through the development of project ideas, data collection and management, psychometric expertise, and methodological discussions.

Emily Barlow-Krelina, the first author, developed the conceptual rationale for the study, collected, analyzed and interpreted the data. She was also the primary contributing author to the manuscript, producing the initial draft and completing all major revisions.

4.2 Abstract

Objective. We examined the association between cognitive reserve (CR; estimated via parental education) and cognitive function in youth and young adults with pediatric-onset multiple sclerosis (POMS) relative to age-matched healthy controls. This relationship was specifically examined for tasks on which POMS patients previously demonstrated cognitive deficits.

Methods. Sixty-seven patients with POMS (age range: 8-29 years) and 95 controls completed the Penn Computerized Neurocognitive Battery and the oral version of the Symbol Digit Modalities Test. A multiple regression was conducted for each cognitive outcome (working memory, attention/inhibition, verbal memory, visuospatial processing, verbal reasoning, overall response time, and processing speed), consisting of: (1) Group; (2) CR, and (3) a Group x CR interaction. Simple effects for CR were examined per group where there were significant interactions ($p < .10$).

Results. Higher CR was associated with better performance for all participants on tasks of working memory, verbal memory, visuospatial processing and verbal reasoning, but not with overall response time or processing speed ($p > .05$). CR effects were found to be stronger in POMS patients (age at testing=18.4±3.8 years; age at POMS onset=15.1±2.0 years) relative to controls on tasks of executive functioning (working memory, $p = .05$; attention/inhibition, $p = .03$), with larger performance decrements from controls at lower levels of CR.

Conclusion. Greater CR is associated with better cognitive performance on higher-order cognitive tasks for healthy and MS youth. Furthermore, CR may help to protect against the presentation of executive dysfunction for youth with POMS. These findings point to potential opportunities for protection against the presentation of cognitive deficits in POMS.

4.3 Introduction

Multiple sclerosis is a chronic demyelinating and degenerative condition of the central nervous system (CNS), with 3-5% of cases diagnosed in childhood and adolescence[1]. Cognitive impairment occurs in approximately 30% of youth and young adults with pediatric-onset multiple sclerosis (POMS), with the prevalence and severity of impairment typically increasing as the disease progresses[165]. Deficits are most consistently observed in information processing speed, executive functions, language and memory, and can be of sufficient severity to impact everyday academic and intellectual abilities[101, 103].

The severity of cognitive dysfunction in POMS is associated with a younger age at disease onset, longer disease duration, greater neurological disability, and more severe symptoms of fatigue and emotional distress, however, these relationships are modest and are not consistently found across studies[95, 101-103, 120, 121, 127]. Although MRI measures of MS pathology demonstrate comparatively stronger associations with cognitive outcomes[97, 102], it is noteworthy that a majority of youth and young adults with MS remain cognitively intact despite accruing significant neuropathology[165]. This disconnect between disease burden and cognitive function has been observed in adults with MS and has been termed the 'cognitive-pathologic dissociation', leading to the question of how some individuals can better withstand MS pathology without demonstrating cognitive impairment[166].

Similar dissociations have been observed in a variety of clinical populations, leading to the theory of cognitive reserve (CR)[167, 169]. Stern defines CR as *the adaptability of cognitive processes that helps to explain differential susceptibility of cognitive abilities or day-to-day function to brain aging, pathology, or insult*. In other words, it is posited that individuals will vary in the expression of neuropathology as a consequence of differences in their capacity to adapt to insult. This is believed to occur through two mechanisms: neural reserve and neural compensation[169]. Neural reserve refers to differential efficiency and/or capacity of task-related networks – i.e., the extent to which a network is activated, or has room for upregulation, to complete a task. Conversely, neural compensation refers to the maintenance of functionality through the use of alternate networks – and thus cognitive strategies – when primary task-related networks are compromised.

CR is believed to be determined by innate factors (genetics, in utero exposures), as well as one's participation in physically and cognitively stimulating activities[171]. As such, CR is often measured proximally by sociobehavioural determinants, including years of education, crystallized intelligence, occupational complexity, socioeconomic status, and engagement in cognitive leisure or physical activities.

Since its conception, models of CR have been examined in the context of traumatic brain injury, Parkinson's Disease, HIV-related dementia, and MS[166, 173-175]. Greater literacy, educational/occupational attainment, premorbid IQ, and engagement in cognitive leisure activities have shown positive associations with cognitive outcomes in adults with MS[181-183, 188, 190, 192, 193, 199, 205], and are protective against MS-related changes in processing speed and memory over time[177-179]. Moreover, each of these proxies of CR have shown moderation effects with structural measures of MS pathology, whereby higher CR attenuates the negative relationship between MS disease burden and cognitive outcome[177, 178, 183, 189-193, 205]. In line with theories on the mechanisms for CR, patients with greater vocabulary knowledge show less recruitment of task-related regions during working memory processing, suggesting that greater CR may be associated with greater network efficiency, thus increasing the capacity for compensatory upregulation in the context of injury[198].

Research on CR has been comparatively limited in pediatric populations and warrants further investigation, as reserves may manifest differentially in response to pathology accrued during periods of neurocognitive maturation. Further, methodological challenges arise with the measurement of CR in youth. Proxies such as educational/occupational attainment are not appropriate in the context of ongoing academic and vocational pursuits. Similarly, typical estimates of premorbid IQ, such as measures of word knowledge, are confounded by age in pediatric cohorts.

In POMS, CR has been estimated by parental education, social status (a composite measure of parental education and occupation), IQ at first assessment, and word knowledge. Of these metrics, IQ at first assessment is most consistently associated with outcomes, showing prediction of more stable or improving trajectories of processing speed and cognitive function overall[128, 224]. Similarly, higher word knowledge has been associated with a reduced risk for cognitive impairment and higher occupational complexity in adults with POMS[132]. Importantly, these measures of CR are confounded by the injury itself, leaving it unclear whether these relationships are attributable early disease severity or shared variance between cognitive measures related to a common *g* factor.

Conversely, parental education may serve as a more effective proxy for CR in youth, given its independence from disease-related factors, and known associations between education level and intellectual functioning, parent and child IQ, and between parental education, socioeconomic status and home environment[231, 232, 235, 236]. Higher parental education is associated with expectations for higher educational attainment in their children, as well as greater opportunities to provide learning-related activities, which in turn have been linked to cognitive outcomes[236, 237].

Moreover, it is possible that higher parental education may be associated with greater access to or uptake of remedial resources post-injury[261, 262].

In POMS, Till and colleagues[95] found that youth with higher educated parents were more likely to show stable or improving cognitive performance over a 1-year period, after adjusting for age at testing, age at onset, disease duration, sex, change in mood-related symptoms, IQ at first assessment, and neurological disability. Conversely, Charvet and colleagues found no effect for parental education on risk for decline on one or more tasks[114], and maternal education was not predictive of clinically meaningful decline in processing speed in a study by Wallach and colleagues[129]. Given the holistic assessment of cognitive outcome in these studies, as well as the potential for limited CR effects in simple processing speed[188], further assessment of CR is warranted in POMS, with examination of potential domain-specificity. Moreover, comparison to healthy controls (HCs) is needed to clarify to what extent CR facilitates adaptation to deficit in POMS, over and above normative variation in cognitive function resulting from enrichment factors.

In the current study, we sought to examine CR across a breadth of neurocognitive functions in POMS, and relative to age-matched healthy controls, using parental education as a proxy. Given prior evidence for associations between CR and cognitive outcomes in healthy youth[168, 172], we anticipate CR effects will be observed across all participants. CR effects are, however, expected to be most apparent for participants with POMS, and for tasks on which patients demonstrate greater neurocognitive deficit, given the greater need for adaptive use of CR.

4.4 Method

Participants. Youth with demyelinating syndromes were enrolled between 2004 and 2019 through the Canadian Pediatric Demyelinating Disease Study (CPDDS), a multi-site, longitudinal study including 23 sites across Canada and the Children's Hospital of Philadelphia as described in Barlow-Krelina and colleagues[263]. Patients with monophasic demyelination, those identified as having MOG-related demyelination, anti-AQP4-related neuromyelitis optica spectrum disorder, or non-demyelinating disease were excluded. HCs were enrolled between 2015 and 2019 using flyers and web-based advertising.

All English-speaking participants engaged in the CPDDS between December 2015 and June 2019 were offered neurocognitive testing. Research ethics approval was obtained by all participating institutions. Written informed consent was obtained from participants or a parent/legal guardian.

Measures. Demographics, developmental milestones, and medical histories were obtained using standardized case report forms. Neurological findings were documented by study site neurologists, leading to the determination of an approximated Expanded Disability Status Scale score (EDSS[57])[89]. Symptoms of emotional distress were measured using the Pediatric Index of Emotional Distress (PI-ED[251]) and the Hospital Anxiety and Depression Scale (HADS[252]) for participants below and at/above age 16 years, respectively. A score greater than 20 is indicative of clinically significant emotional distress[251, 252]. Self- and parent-reported fatigue were measured using the PedsQL Multidimensional Fatigue Scale[253]. Social status was measured by the Barratt Simplified Measure of Social Status (BSMSS)[254].

Cognitive evaluation. Participants completed the oral version of the Symbol Digit Modalities Test (SDMT)[255] and the Penn Computerized Neurocognitive Battery (PCNB)[256], a computerized assessment tool consisting of 15 tests across five broad domains of function (Table 1): executive function, episodic memory, complex cognition, social cognition, and sensorimotor speed. The PCNB was initially developed to measure neurocognitive function using tests validated with functional neuroimaging[149], and has demonstrated sensitivity for detecting neurocognitive dysfunction in youth with neuropsychiatric and medical conditions[151-154].

All assessors completed a standardized training protocol for administration of the PCNB. The battery was administered in a single session of approximately one hour, with breaks offered at three standard intervals. Data underwent quality control procedures, including: identification of outliers for response time and multiple key-presses, as well as examination of assessor comments on behavior observations and/or environmental distractions pertinent to testing. Invalid participant data were excluded.

Each task provides a measure of both accuracy and response time, with the exception of sensorimotor tests specifically designed for measuring speed. Raw scores for each outcome were standardized into *Z*-scores based on the means and standard deviations (SD) of the HCs. *Z*-scores were calculated from four age bands (i.e., 8-10, 11-13, 14-17, ≥18 years), which were determined based on the developmental curves for the PCNB tasks and with consideration of the number of participants in each group. Response time scores were transformed, so that higher *Z*-scores reflect better performance (i.e., shorter response times).

The current analyses follow from a prior examination of the neurocognitive profile in the same cohort[263]. Our analyses are thus focused on the neurocognitive tasks on which MS participants were observed to have moderate performance deficits relative to HCs, with statistical significance at $p < .05$. This includes accuracy on the Letter N-back (working memory), Go-No-Go

(attention/inhibition), Verbal Memory, Line Orientation (visuospatial) and Verbal Reasoning tasks, overall response time on the PCNB, and performance on the SDMT (processing speed).

Cognitive Reserve. CR was estimated by the average number of years of education completed by the parents of each participant. Participants self-reported this value for each of their parents. These data were then cross-checked with the level of schooling reported by parents on the BSMSS (e.g., High School, College, etc). Years of parental education were imputed if available only on the BSMSS (17 participants). Parent reports on the BSMSS were also used if discrepant with participant reports by more than 3 years (i.e., approximate difference of one category-level of education; 11 participants). BSMSS categories were converted to years of education as follows: partial high school (10^{th} or 11^{th} grade) = 11 years, high school = 12 years, partial college = 14 years, college/university = 16 years, graduate degree = 18 years.

Data Analysis. We used one-way analysis of variance (ANOVA), Mann-Whitney U, or chi-squared (X^2) tests to compare the POMS and HC groups on demographic variables, as well as on fatigue and emotional distress scores. Clinical variables were summarized using descriptive statistics. CR was examined in association to demographic and clinical variables by Spearman correlations or ANCOVA/Mann-Whitney U tests. For all PCNB scores, outliers were Winsorized to 3 SD from the mean; this was done for <2% of all values. All analyses were performed using IBM SPSS Statistics version 24 (Armonk, NY: *IBM* Corp).

Statistical analyses were performed separately for each age-normed (i.e., *Z*-score) dependent variable: accuracy on the Letter N-back, Go-No-Go, Verbal Memory, Line Orientation and Verbal Reasoning tasks, overall response time on the PCNB, and performance on the SDMT. A multiple regression was conducted for each outcome, consisting of: (1) Group; (2) CR, and (3) a Group x CR interaction term. CR was centered at its mean to reduce multicollinearity between CR and the interaction term. Analyses were adjusted for task-specific response time/accuracy. Effect sizes were determined using a partial eta-squared (η^2).

We probed simple effects for CR when Group x CR interactions showed a p-value < .10 [264]. We performed multivariable linear regression analyses to examine the association between CR and the cognitive outcome per group, adjusting for task-specific response time/accuracy.

4.5 Results

Of the 80 eligible POMS patients and 139 HCs in the CPDDS, neurocognitive data were obtained for 67 (83.7%) POMS patients and 95 (68.3%) HCs (see Figure 3). We excluded one patient due to significant visual/motor impairment, one patient due to impact of intravenous therapy

on response times, and one HC due to their expressed familiarity with the assessment battery. Among the 94 HCs with valid data on the PCNB, we excluded 18 participants who were 13 years and younger to enhance age-matching between the groups. The retained HCs were selected at random, after matching to the four MS participants in the 8-13 age range based on their age and sex. Data were also excluded from the current analyses for four POMS patients and two HCs due to incomplete CR data.

The final sample of 61 POMS patients and 74 HCs were well-matched with regards to age, sex, level of education and social status (*p*'s > .05), however, parental education (i.e., CR) was moderately lower in POMS patients (*p* = .06). While POMS patients did not differ from HCs with regards to their risk for clinically elevated emotional distress or level of self-reported fatigue (*p* > .05), youth with POMS had higher parent-reported fatigue relative to HCs. Clinical and demographic characteristics of the sample are described in Table 4.

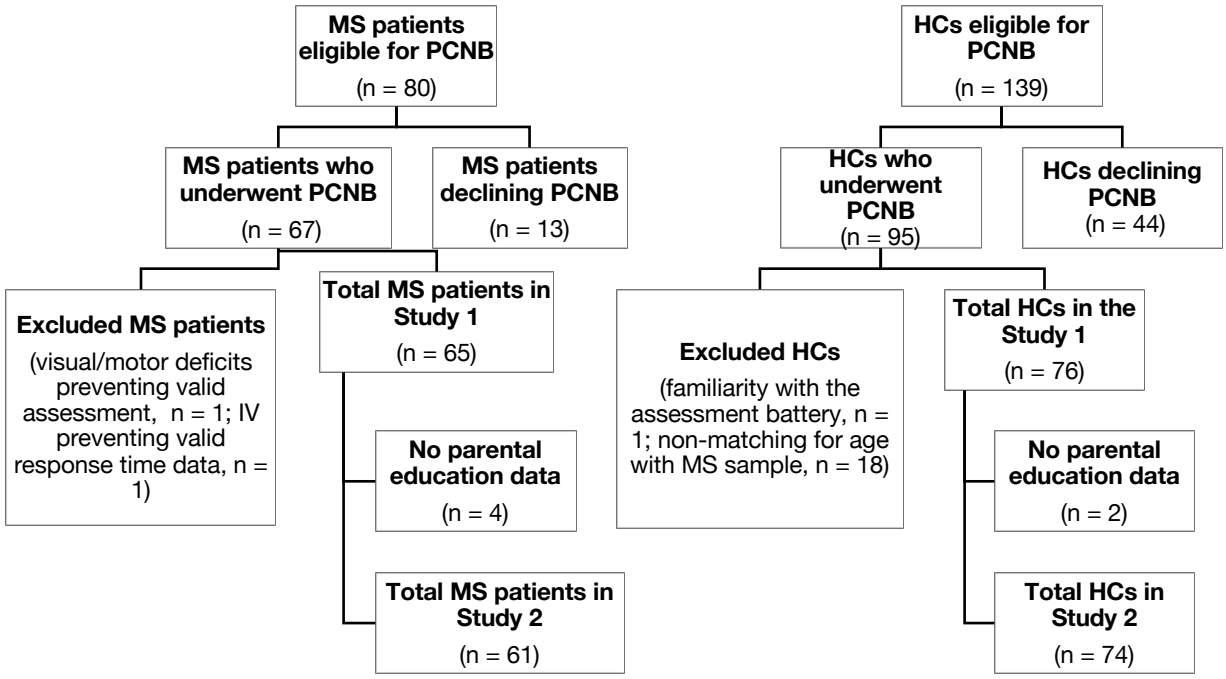

Figure 3. Patient enrollment from the Canadian Pediatric Demyelinating Disease Study for Study 2.

Table 4. Demographic and clinical characteristics of pediatric-onset MS and healthy control participants in Study 2

	MS (n=61) M ± SD (range) / N (%)	**HC (n=74)** M ± SD (range) / N (%)	***p***
Age at testing (years)	18.4 ± 3.8 (10-27)	18.2 ± 4.6 (8-29)	.61
Sex (#female, %female)	44 (72.1)	48 (64.9)	.37
Participant education (years)	12.0 ± 2.9 (5-19)	12.2 ± 3.6 (3-20)	.32
Parental education	14.3 ± 1.9 (10-19)	15.0 ± 2.3 (10-20)	.06
Socioeconomic status	39.8 ± 14.1 (12-66)	43.1 ± 14.4 (8.5-66)	.21
Nationality (#Canadian, %Canadian)	46 (75.4)	56 (75.7)	.97
Emotional Distress† (#high, %high)†	6 (10.2)	3 (5.1)	.31
Participant Fatigue			
Parent-rated	69.7 ± 20.7 (33.3-100)	83.9 ± 14.8 (45.8-100)	**.004**
Participant-rated	64.0 ± 20.8 (26.4-98.6)	73.9 ± 14.3 (43.1-100)	.10
Age at disease onset (years)	15.1 ± 2.0 (7.3-17.9)	-	-
Disease Duration (months)	44.9 ± 46.4 (0-133)	-	-
EDSS (median, range)	1.5 (0-6.5)	-	-
DMT (#Y, %yes)	49 (80.3)	-	-
DMT duration† (months; median, range)	34 (0-123)	-	-

Abbreviations: MS = multiple sclerosis; HC = healthy control; EDSS = Expanded Disability Status Scale; DMT = Disease Modifying Therapy

Note. Emotional distress was measured by the Pediatric Index of Emotional Distress and Hospital Anxiety Depression Scale, each of which generate emotional distress scores based on a combined depression and anxiety score. A score greater than 20 is indicative of clinically significant emotional distress[251, 252]. Emotional distress scores were not available for 2 POMS patients and 16 controls. Fatigue was measured by the PedsQL Multidimensional Fatigue Scale; scores range from 0-100, with higher scores reflecting fewer problems[253]. Self-reported fatigue was not available for 2 POMS patients and 7 controls; parent-reported fatigue was not available for 10 POMS patients and 22 controls. Social status was measured by the Barratt Simplified Measure of Social Status, which yields a total education and occupation score between 8-66 for parents/guardians[254].

Cognitive Reserve Effects. Examining across all participants, higher CR was associated with lower self- and parent-reported fatigue (*rho* = -0.23, $p = .01$ and $r = -0.25$, $p = .01$, respectively), as well as with fewer self-reported symptoms of emotional distress (*rho* = -0.20, $p = .03$). No associations were observed between CR and the demographic or disease variables ($p > .05$).

Working Memory. POMS participants performed less accurately than HCs on the Letter N-back task (Estimated marginal mean ± SE: MS = -0.84 ± 0.17, HC = -0.01 ± 0.15; $p < .001$; Table 5). Participants with higher CR demonstrated more accurate Letter N-Back performance ($p = .004$). Moreover, there was a Group x CR interaction ($p = .05$), with MS patients showing a stronger CR effect ($B = 0.26$, 95% CI: 0.05, 0.47, $p = .02$) relative to HCs ($B = 0.06$, 95% CI: -0.04, 0.16, $p = .24$; Figure 4A). For participants with lower CR (i.e., one SD below the mean = 12.5 years parental education), working memory performance was 1.27 SD units lower in the POMS group relative to HCs. At higher CR (i.e., one SD above the mean = 17.0 years parental education), the difference between groups is lessened, with the POMS group performing 0.39 SD units lower than HCs.

Attention/Inhibition. POMS participants performed less accurately than HCs on the Go-No-Go task (MS = -0.73 ± 0.18, HC = -0.02 ± 0.16; $p = .002$; Table 5). Although a main effect of CR was not observed ($p = .23$), the Group x CR interaction was significant for the Go-No-Go task ($p = .03$; Table 5). Although the adjusted relationship between CR and accuracy on the Go-No-Go was not statistically significant for either group, this association appeared stronger for MS patients ($B = 0.20$, 95% CI: -0.04, 0.43, $p = .10$) relative to HCs ($B = -0.05$, 95% CI: -0.15, 0.05, $p = .36$; Figure 4B). POMS participants demonstrated attention/inhibition performance 1.27 and 0.34 SD units lower than HCs at low and high CR, respectively.

Verbal Memory. POMS participants performed less accurately than HCs on the Verbal Memory task (MS = -0.62 ± 0.14, HC = -0.02 ± 0.13; $p = .002$; Table 6). Participants with higher CR demonstrated more accurate verbal memory performance ($p = .009$). No Group x CR interaction was observed ($p > .05$; Figure 4C).

Visuospatial. POMS participants performed less accurately than HCs on the Line Orientation task (MS = -0.71 ± 0.15, HC = -0.03 ± 0.13; $p < .001$; Table 6). Participants with higher CR demonstrated more accurate visuospatial performance ($p = .05$). No Group x CR interaction was observed ($p > .05$; Figure 4D).

Verbal Reasoning. POMS participants performed less accurately than HCs on the Verbal Reasoning task (MS = -0.45 ± 0.16, HC = -0.01 ± 0.14; $p = .04$; Table 6). Participants with higher CR demonstrated more accurate verbal reasoning performance ($p = .05$). No Group x CR interaction was observed ($p > .05$; Figure 4E).

Table 5. Multiple regression analysis for variables predicting executive function *Z*-scores

Variable	Letter N-Back				Go-No-Go			
	B	**SE *B***	***β***	***p***	***B***	**SE *B***	***β***	***p***
Response Time	0.12	0.10	0.09	.25	-0.39	0.11	-0.29	**<.001**
Group	-0.83	0.22	-0.31	**<.001**	-0.75	0.24	-0.25	**.002**
Cognitive Reserve	0.16	0.05	0.25	**.004**	0.07	0.06	0.10	.23
Group x Cognitive Reserve	0.20	0.11	0.16	.05	0.25	0.12	0.18	**.03**
R^2			.19				.18	
F			7.35	**< .001**			7.00	**< .001**

Note. Healthy controls were coded as the reference group for the group comparison (HC = -0.5, MS = 0.5).

Table 6. Multiple regression analysis for variables predicting Verbal Memory, Line Orientation, and Verbal Reasoning *Z*-scores

Variable	Verbal Memory				Line Orientation				Verbal Reasoning			
	B	**SE *B***	***β***	***p***	***B***	**SE *B***	***β***	***p***	***B***	**SE *B***	***β***	***p***
Response Time	0.20	0.08	0.20	**.02**	-0.12	0.10	-0.11	.21	0.07	0.12	0.05	.57
Group	-0.60	0.19	-0.26	**.002**	-0.68	0.20	-0.29	**<.001**	-0.44	0.21	-0.18	**.05**
Cognitive Reserve	0.12	0.05	0.22	**.009**	0.09	0.05	0.17	**.05**	0.10	0.05	0.19	**.04**
Group x Cognitive Reserve	0.05	0.09	0.04	.61	-0.12	0.10	-0.07	.44	0.05	0.10	0.04	.64
R^2			.21				.14				.08	
F			8.53	**< .001**			5.14	**.001**			2.81	**.03**

Note. Healthy controls were coded as the reference group for the group comparison (HC = -0.5, MS = 0.5).

Table 7. Multiple regression analysis for variables predicting PCNB Response Time and SDMT *Z*-scores

Variable	PCNB Response Time				SDMT			
	B	**SE *B***	***β***	***p***	***B***	**SE *B***	***β***	***p***
Accuracy	-0.20	0.08	-0.25	**.009**				
Group	-0.29	0.10	-0.27	**.003**	-0.42	0.19	-0.20	.03
Cognitive Reserve	0.03	0.02	0.13	.16	0.07	0.05	0.16	.11
Group x Cognitive Reserve	0.02	0.04	0.04	.69	0.04	0.09	0.06	.69
R^2			.09				.07	
F			3.26	**.01**			2.91	.04

Note. Healthy controls were coded as the reference group for the group comparison (HC = -0.5, MS = 0.5). SDMT data was not available for 6 POMS patients and 15 HCs.

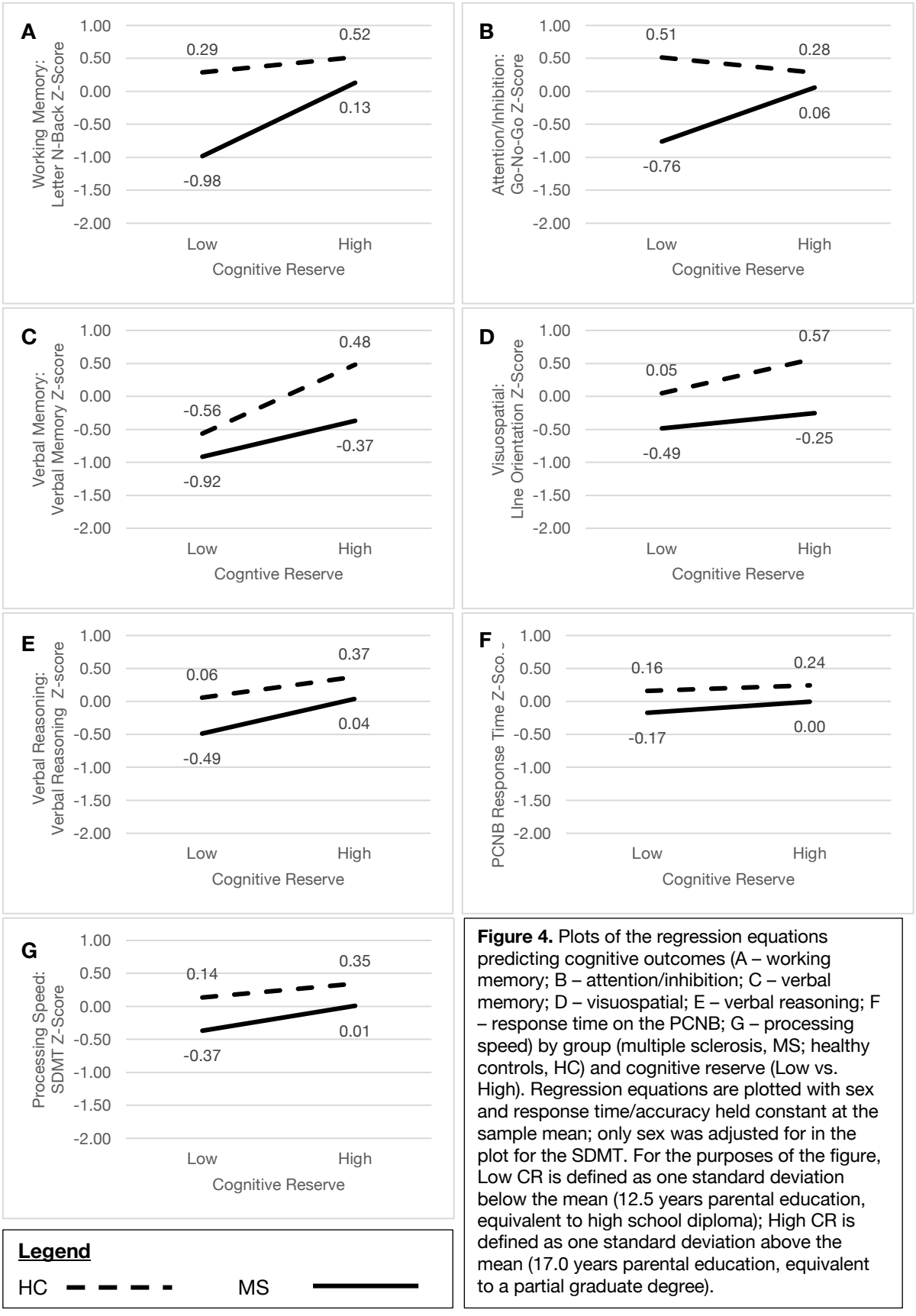

Figure 4. Plots of the regression equations predicting cognitive outcomes (A – working memory; B – attention/inhibition; C – verbal memory; D – visuospatial; E – verbal reasoning; F – response time on the PCNB; G – processing speed) by group (multiple sclerosis, MS; healthy controls, HC) and cognitive reserve (Low vs. High). Regression equations are plotted with sex and response time/accuracy held constant at the sample mean; only sex was adjusted for in the plot for the SDMT. For the purposes of the figure, Low CR is defined as one standard deviation below the mean (12.5 years parental education, equivalent to high school diploma); High CR is defined as one standard deviation above the mean (17.0 years parental education, equivalent to a partial graduate degree).

PCNB Response Time. POMS participants demonstrated slower overall PCNB response time relative to HCs (MS = -0.24 ± 0.07, HC = 0.05 ± 0.06; p = .003; Table 7). No CR main effect or Group x CR interaction were observed for PCNB response time (p > .05; Figure 4F).

SDMT. POMS participants demonstrated slower processing speed relative to HCs on the SDMT (MS = -0.39 ± 0.14, HC = 0.03 ± 0.13; p = .03; Table 7). No CR main effect or Group x CR interaction were observed for the SDMT (p > .05; Figure 4G).

4.6 Discussion

We examined CR across a range of neurocognitive functions found to be affected in youth and young adults with POMS, using parental education as a proxy for reserve. In line with our prior research on the same cohort and existing literature in POMS, our MS participants demonstrated reduced accuracy on tasks of working memory, attention/inhibition, verbal memory, visuospatial ability and verbal reasoning, as well as slower response time and simple processing speed relative to controls[165, 263]. Associations between CR and cognitive function were found for all participants on tasks of verbal memory, visuospatial ability and verbal reasoning, but not for response time or simple processing speed. Moreover, we found evidence suggesting protective effects of CR in the context of executive dysfunction in POMS, with MS patients showing poorer performance overall, as well as a greater discrepancy from controls at lower CR relative to higher CR.

Given CR's proposed role in *adaptation* to pathological change, it is notable that CR effects were stronger for POMS participants relative to controls on tasks of executive function, and for working memory in particular, wherein rates of impairment were highest (i.e., 35.5%[263]). These interaction effects, however, appear to be driven by a lack of association between CR and executive function in HCs. Given that controls with higher CR obtained near-perfect performance on the executive function tasks (average accuracy for HCs was 96% and 97% for the Letter N-Back and Go No-Go tasks, respectively), ceiling effects may have masked a more generalized association for CR and executive functions across participants. Despite this, the presentation of *deficit* is moderated by CR in POMS. These findings are in line with the expectation that adaptive CR mechanisms will be most apparent in the context of MS where there is suspected damage to functional networks and thus a need for compensation.

Among the proposed mechanisms for CR are *neural reserve* – referring to individual differences in network efficiency and/or capacity – and *neural compensation*, which refers to the maintenance of functionality through the use of alternate strategies[168]. We previously demonstrated fMRI evidence of greater activation in working memory networks in a cohort of

cognitively-preserved youth and young adults with POMS, relative to HCs[239], providing evidence for neural reserve as a potential mechanism for CR. Although these fMRI data were not tied to sociodemographic proxies of CR, higher engagement in physical activity was associated with larger whole-brain grey and white matter volumes[242]. In cognitively intact adults with MS, studies have shown both greater and more extensive activation compared to HCs during working memory processing[206-209, 211, 214, 215]. Moreover, Sumowski and colleagues[198] isolated a pattern of activation associated with greater CR across conditions of a working memory task (i.e., lesser prefrontal recruitment, lesser deactivation of the default mode network), whose expression almost fully mediated the relationship between CR and behavioural performance.

Importantly, relationships between CR and cognitive outcome do not exist *only* as a function of adaptation to neuropathology, but can occur outside of the context of disease models. For instance, one's general level of cognitive ability is related to changes in neural activity as subjects move from low to high levels of task demand[168, 172]. We found that both POMS and control groups showed CR effects for tasks of verbal reasoning, visuospatial ability and verbal memory. This is contrasted against prior findings by Sumowski and colleagues[188], who showed that CR effects were stronger for adult MS participants relative to controls on tasks of verbal learning and memory, leading to comparable performance between groups at high CR. Given the more modest CR effects observed in the current study, it is possible that CR may provide less effective protection for individuals with earlier versus later MS onset; however, direct comparisons between individuals with pediatric and adult-onset MS are needed to confirm if and how these effects differ. Importantly, although the associations between CR and these cognitive outcomes were not stronger in participants with POMS, CR may still afford protection from these deficits in the context of CNS disease.

We found no CR effects on measures of simple processing efficiency and response time for POMS participants nor controls. These findings are similar to Sumowski and colleagues[188], and are consistent with Krieger and Sumowski's[219] proposal that reserves will vary as a function of a network's capacity for organizational plasticity. Reserves are anticipated to be greatest for higher-order functions, where there are more redundancies in networks or interpersonal variability in how tasks are processed, and to be comparatively limited for functions relying on more linear structures with fewer redundancies (e.g., motor/sensory systems, simple processing speed). Although there may be potential for alternative strategy use on tasks of simple cognitive processing speed, the range of possible approaches is more restricted and any alternate approaches are likely to be less efficient than the automatic strategies otherwise taken. Consistent with this theory, relationships between MRI markers of MS pathology and cognitive outcomes are typically stronger for tasks of

simple processing efficiency as compared to other cognitive tasks[97, 102, 265, 266], where CR may better moderate its expression.

CR was estimated by parental education, given its unique relation to both heritable and environmental enrichment factors[231, 232, 235, 236]. While CR was not correlated with disease-related factors in POMS, we found associations between higher CR and fewer symptoms of fatigue and emotional distress across all participants. As parental education has been associated with psychosocial aspects of the home environment[236], and symptoms of fatigue and low mood have the potential to impact cognitive function[267, 268], it is possible these findings highlight a mechanism by which CR could facilitate better cognitive functioning. By contrast, better cognitive functioning associated with higher parental education may help to reduce symptoms of fatigue or emotional distress[58]. Further research is needed to elucidate the nature of these associations.

Although parental education is largely invariable for a person over time, CR itself is not conceptualized as a fixed premorbid factor[168]. On the contrary, an extensive literature on cognitive rehabilitation highlights the potential for enhancement of function through engagement in cognitive activities post-injury. Parental education is thus limited as a measure of CR, as it does not directly measure a person's engagement in cognitively-enriching activities, nor does it capture how this might increasingly vary from one's childhood home environment as they become a young adult. Future research examining CR effects may benefit from examining this construct at several angles (i.e., premorbid vs. post-injury/disease, cognitive vs. physical, occupational/educational vs. leisure activities) to more robustly estimate CR, as well as to assess the unique contributions of each CR factor to cognitive outcomes.

We show that CR may be protective against the presentation of executive dysfunction in POMS patients. CR was also associated with better performance on tasks of verbal memory, visuospatial ability and verbal reasoning for all participants. These findings highlight the potential role of one's environment for shaping one's adaptability to POMS, however, research incorporating structural and fMRI measures are needed to confirm the role of CR in moderating the expression of neuropathology in POMS. Longitudinal studies including people with pediatric and adult-onset MS are also needed to clarify whether the efficacy of CR depends on one's developmental stage and how CR behaves as MS neuropathology is accrued. These future clarifications on the scope, mechanisms, and essential components contributing to CR are recommended with the goal to inform approaches for prevention or rehabilitation of cognitive dysfunction in POMS.

Chapter 5: Discussion

5.1 Overview of studies

In this dissertation, we sought to further clarify the profile of cognitive functioning in POMS using a computerized tool to delineate the role of processing speed from a range of cognitive deficits, and to examine the protective effects of CR against the presentation of found deficits. The cognitive sequelae of POMS were examined in 67 youth and young adults with POMS, contrasted against 95 controls, using the Penn Computerized Neurocognitive Battery. CR was examined using parental education, given known associations to heritable and environmental factors contributing to cognitive outcomes and its independence from disease-related factors. CR effects were examined relative to HCs to distinguish covariance related to adaptation to injury from normative associations between cognitive function and enrichment factors.

5.2 Summary of results

The results of Study 1 (Chapter 3) found reduced accuracy in youth and young adults with POMS on tasks of working memory, response inhibition, verbal recognition memory and visuospatial processing, as well as slowed overall response time. In line with prior research, accuracy performance was also moderately poorer for patients with POMS on a task of verbal reasoning, and information processing speed was slower on the SDMT, however, these group differences did not meet our statistical threshold. While performance on the SDMT was associated with overall performance on the PCNB, criteria for impairment based on each of these metrics identified somewhat distinct subsets of patients as cognitively impaired. Moreover, group differences in task accuracy were found after adjusting for response time, suggesting that these aspects of cognitive dysfunction exist over and above slowed information processing speed in youth with MS. While having a longer history of POMS was associated with poorer performance on tasks of visuospatial processing and verbal memory, no other correlations were found between disease-related factors (age at onset, disease duration, symptoms of emotional distress, self- and parent-related fatigue) and the cognitive deficits measured on the PCNB.

In Study 2 (Chapter 4), it was found that higher CR (i.e., parental education) was associated with more accurate performance for all participants on tasks of working memory, verbal memory, visuospatial ability and verbal reasoning, but not for response time or simple processing speed. Notably, the CR effect was shown to a greater extent in POMS patients relative to controls for tasks of executive function (working memory, attention/inhibition), with MS patients showing a greater discrepancy from controls at lower CR relative to higher CR. This greater CR advantage for POMS patients was not found for other domains of cognitive function.

5.3 General discussion

Information Processing in POMS. The cognitive sequelae of POMS have been studied in some depth, with evidence for cognitive impairment in approximately 30% of youth and consistent impacts on processing speed, attention and executive functioning. Of note, slowed information processing speed has been a particular focus of study in MS, with theories positing that difficulties in this area represent a core deficit upon which others are contingent.

Complexities arise regarding the definition and measurement of processing speed when this construct is examined more closely in MS. Costa and colleagues[243] summarized several definitions that have been put forward, including those which define processing speed as (1) the amount of time needed to execute a task or the amount of work completed within a certain period, (2) a complex construct resulting from the interaction of multiple factors, and (3) those which define processing speed physiologically, referring to the speed with which the brain can process information. A number of theories have been put forth to facilitate our understanding of processing speed in MS as well, including the (1) *Relative Consequences Model*, (2) *Independent Consequences Model*, (3) *Limited Time Mechanism*, and (4) *Neural Noise Hypothesis*. These theories are not all mutually exclusive, but rather explain the construct from different perspectives. They have, however, been discussed almost exclusively regarding adults with MS, leading to questions of their relevance in developmental contexts.

While the *Relative Consequences Model* suggests that slowed processing speed is the primary deficit in MS, which in turn leads to other areas of cognitive difficulty, the *Independent Consequences Model* indicates that deficits in processing speed are independent from but not mutually exclusive to other areas of deficit[137]. The *Neural Noise Hypothesis* attempts to explain deficits in information processing from a neurobiological perspective, postulating that processing speed is dependent on the signal-to-noise ratio in the brain[269]. While this mechanism has not been formally clarified at this point in time, it has been proposed that damage to widespread white matter tracts impacts the coordinated firing of functional networks broadly[270]. Moreover, the *Limited Time Mechanism* suggests that slowed processing speed contributes to deficits in higher-order functions due to a limited time within which information can be processed for a task[136]; in other words, early information is degraded and impoverished before it can be integrated with later information, leading to impaired cognitive functioning beyond slowing of speed of processing.

Importantly, processing speed at the simplest level requires efficient functioning of (1) sensory, (2) cognitive, and (3) motor processes[243]. Given the impacts of MS on sensory and motor tracts, as well as widespread white matter networks, it is unsurprising that processing speed represents a core deficit in MS. However, as suggested by the *Independent Consequences Model,*

the presence of slowed information processing as an independent and contributing deficit in the neuropsychological profile of POMS does not exclude the possibility of other areas of difficulty which represent deficits over and above slowed information processing. In the first study, we observed the latter, with accuracy deficits in working memory, response inhibition, verbal recognition memory, visuospatial processing and verbal reasoning after controlling for variations in response time.

Pulling from neurobiological literature, simple processing speed may be conceptualized as a true "information processing function" of the brain which relies on the speeded potentiation of action potentials down the axon. As such, it is anticipated that injury to white matter tracts broadly, via demyelination and Wallerian degeneration, leads to more disrupted neuronal communication. Indeed, slower processing speed is demonstrated in youth and adults with MS who demonstrate reduced white matter integrity[135].

While there has been some lack of clarity in the literature regarding the distinction of simple and more complex tasks of information processing, which begin to overlap with higher-order executive functioning tasks (e.g., the PASAT), we posit that these are distinct constructs. While true information processing speed does not have an associated neural network per se, higher-order neuropsychological functions require the coordinated action of disparate and functionally-specific brain regions. As such, while slowed information processing necessarily impacts other areas of cognitive function (such as by the *Limited Time Mechanism*), the observation of dysfunction in other cognitive domains that are statistically independent from slowed information processing may be explained by impacts to functionally-specific brain areas, such as through injury to grey matter, as has been observed in MS and POMS alike. Moreover, in line with the *Neural Noise Hypothesis*, it is plausible that impacts to processing speed in developing youth is disruptive to healthy development of cognitive functions more broadly, and of reserves, in turn.

Neuropsychological Assessment in POMS. Despite the prevalence of cognitive difficulties and the impact of such dysfunction on the everyday functioning and quality of life of persons with MS, cognitive monitoring is not always part of the standard of care, due to practical challenges associated with providing one-on-one testing with trained psychometrists for patients in clinic[271]. However, members of the National MS Society recently provided consensus recommendations for neuropsychological *screening* for all patients who demonstrate clinical or MRI evidence of neurological damage consistent with MS[244]. Cognitive screening entails a focused assessment examining key domains of cognitive function that sufficiently capture the neuropsychological profile of a clinical population to identify individuals affected by its cognitive symptomatology. A subset of

affected individuals then typically receives a more thorough cognitive follow-up to assess areas of need and clarify recommendations. While screeners are understood to be imperfect assessments, this approach is often applied to streamline resources while still providing more comprehensive services to those in need.

As such, Kalb and colleagues[244] recommended that patients with MS be provided with early baseline screening using the SDMT, as a minimum, and that this screening be followed by annual re-assessment with the same tool to enable evaluation of progression in cognitive symptoms, detection of disease activity, and/or assessment of treatment effects. Further neuropsychological evaluation was recommended for pediatric patients with unexplained changes in school functioning, as well as for adults who test positive on the initial screen or if they demonstrate significant cognitive decline (e.g., a change of 0.5 SD).

While there are no clear guidelines for screening for cognitive dysfunction in POMS specifically, it has been proposed that the SDMT may be adequate, with 77% sensitivity and 81% specificity in detecting impairment based on more comprehensive neuropsychological assessment[111]. However, given the breadth of cognitive dysfunction that we found to exist independently of slowed information processing speed in youth and young adults with POMS, as well as the distinct groups of patients identified as cognitively impaired based on the PCNB (29%) versus the SDMT alone (17%), we posit that limiting the scope of cognitive screening in this way would fail to capture an important subset of youth who are experiencing cognitive difficulties.

The PCNB offers efficient measurement of the neuropsychological profile of POMS more broadly, including measures of executive functioning, verbal and fluid reasoning, visuospatial ability, verbal and visual memory, and social cognition, along with delineation of processing speed from accuracy. However, it's utility as a cognitive screener remains unclear, as it was not assessed alongside a full clinical neuropsychological battery. We provided evidence for discriminant and concurrent validity of the PCNB in POMS via our replication of known group differences in cognitive function and our demonstration of associations between the PCNB and the SDMT. Importantly, the PCNB remains limited in its assessment of neurocognitive dysfunction in youth with POMS, as data are not available on visuomotor integration or verbal and visual recall. While these areas of function are beyond the intended scope of the battery, they represent common areas of difficulty for youth with POMS, and likely limit the use of the PCNB as a screener. Moreover, while there are well-established American norms available for standardization of scores, the PCNB's clinical utility is currently limited in reporting age-normed scores for Canadian youth. The PCNB is thus effective in measuring cognitive dysfunction in POMS, but needs further evaluation to clarify its potential role in clinical contexts.

Cognitive Reserve in a Developmental Context. We observed associations between higher CR (i.e., parental education) and better cognitive function in healthy and MS youth, as well as evidence for protective effects against the presentation of executive dysfunction in youth with POMS. No CR effects were observed for measures of processing speed, however, and the larger associations observed between CR and executive functions in POMS patients were found in the context of potential ceiling effects in controls.

From the outset of the study, it was hypothesized that associations between CR and outcomes would be stronger in POMS patients relative to controls, in line with findings from prior studies in adults with MS. Sumowski and colleagues[188] found cognitive deficits only in MS patients with lower CR, and that MS patients with high CR showed comparable performance to controls, suggesting that reserves may facilitate adaptation to injury to the extent that functioning is preserved. By contrast, we observed better performance in POMS patients with higher CR, though performance decrements were still apparent relative to controls at high CR on most cognitive outcomes (verbal memory, verbal reasoning, visuospatial processing). Moreover, while high CR POMS patients performed similarly to controls on tasks of executive functioning, the potential for ceiling effects on these tasks highlight the possibility that high CR POMS patients might show deficits in these areas at greater levels of task demand. Thus, while benefits of CR are maintained in the context of MS, it is not clear whether the protective effects of CR are sufficient to prevent the presentation of cognitive symptoms in youth and young adults with POMS. Similar to controls, POMS patients with greater CR show better cognitive performance, and high CR POMS youth are less likely to meet *absolute* criteria for cognitive impairment (i.e., -1.5 SD below the mean), however, given the comparability of performance decrements from controls across levels of reserve for many tasks, it appears that youth with POMS continue to be at risk for neurocognitive deficits relative to their expected level of performance despite high CR. Importantly, we found that the degree of protection afforded by CR appears to be domain-specific, with greater potential for compensation on higher-order executive functions relative to tasks of simple information processing speed.

Prior research examining CR in POMS has given mixed results, with evidence for protective effects in some studies but not others[113, 114, 121, 127-129, 132, 224]. Till and colleagues [95] found that youth with higher educated parents were more likely to show stable or improving performance on a cognitive battery over 1 year, though these youth still demonstrated deficits relative to controls and failed to show age-expected levels of cognitive development in most domains assessed. Moreover, our team found that cognitively intact POMS participants (i.e., those without cognitive impairment) demonstrated enhanced task-related activation relative to controls on a working memory task, suggestive of potential compensatory mechanisms at play[239]. By

contrast, several studies have failed to show associations between parental education and cognitive outcomes in POMS[114, 127], and others have been limited by measures of CR which may be confounded by disease severity (e.g., IQ, word knowledge)[128, 132, 224].

Evidence for CR effects has been substantiated somewhat further in other pediatric populations. Children with pre-existing learning problems have shown worse performance following traumatic brain injury on tasks of attention, learning and memory relative to those without learning problems, and non-injured controls[223]. Similarly, survivors of childhood brain tumors with higher SES show less decline in IQ and academic skills following radiation treatment[272], and survivors of childhood acute lymphoblastic leukemia with higher maternal education show better working memory and verbal memory performance[226]. Of note, Kesler and colleagues[226] found that survivors of leukemia with higher maternal education also had a higher threshold of white matter volume loss prior to the presentation of cognitive deficits, suggestive of potential adaptation to injury afforded by CR. Further evidence for enhanced adaptation afforded by CR in youth was demonstrated by Donders & Kim[273], who found that parental education moderated the expression of verbal comprehension, visuospatial processing and global cognitive difficulties in youth with traumatic brain injury, with more pronounced performance decrements from controls in youth with low CR relative to high CR.

Taken together, these findings provide evidence in support of CR as a protective factor in youth. However, whether a younger age at brain injury impacts the efficacy of reserve mechanisms, and particularly in the context of repeated injury as in POMS, remains in question. A younger age of MS onset has been associated with poorer outcomes in a variety of cognitive domains, including simple processing speed, working memory, and verbal abilities[102, 127, 128]. While these associations are often subtle in cross-sectional studies and were not observed within our group of POMS participants, investigations of long-term clinical progression in adults with early and late-onset MS have illustrated poorer cognitive outcomes for individuals with a pediatric-onset[131, 274, 275]. Adults with POMS have shown faster declines in SDMT performance over time than those with disease onset in adulthood[274], as well as poorer SDMT scores and a higher risk of cognitive impairment cross-sectionally after controlling for disease duration[131, 274, 275]. Moreover, Portaccio and colleagues[132] found that a higher proportion of adult POMS vs adult-onset MS participants achieved a lower educational level compared with that of their parents (13% vs 5%). These results suggest an increased vulnerability for cognitive deficits stemming from an earlier onset of the disease. As cognitive difficulties have been proposed to arise once reserves are exhausted[216], this enhanced vulnerability may result from limits to mechanisms associated with CR or reduced opportunities to build reserves in youth with POMS.

A reduced adaptive ability in POMS could arise as a consequence of impacts of POMS on developing networks. Injury to regions undergoing critical periods of maturation may permanently alter their trajectories of maturation, leading to arrested development, loss of function or later growth into deficit ultimately resulting in reduced functioning relative to age-expectations[220]. In addition, reduced processing efficiency at a young age resulting from widespread demyelination could contribute to greater difficulty coordinating, developing and strengthening cross-cortical networks needed for higher-order functions. In other words, young task-related networks may remain weak with less opportunity to effectively "fire together and wire together", and thus remain less efficient for task processing long-term; this may also help to explain the broader pattern of deficits observed in the current study that were ultimately independent of inefficiency of processing in POMS. Reserves may also be rendered less flexible or varied in individuals affected by POMS due to disruptions to learning opportunities resulting from school absences and rest time that are needed post-relapse. Importantly, given the chronic and relapsing nature of MS, any disruptions to the development of reserves likely occur at several points in time, thus compounding their impact on brain development. This is supported by the observation of smaller head size in youth with POMS relative to age and sex-matched controls[93].

Our results suggest that CR serves to benefit individuals with POMS, but perhaps with limited strength relative to what has been observed in adults. Further study directly examining CR effects in adults with pediatric and adult-onset MS is needed, however, to clarify if and how the age at MS injury impacts the efficacy of these reserve mechanisms. Importantly, challenges with defining proxies of CR in pediatric populations also leads to questions of the role of measurement in limiting the assessment of CR relationships in youth with POMS.

Measurement of Reserve. The construct of reserve was initially summarized in response to the repeated observation that the extent of brain pathology accrued by a person did not directly correspond to the clinical manifestation of that damage[168]. In other words, individuals with similar degrees of brain injury could present as functionally quite different. As such, reserves have been broadly defined as differences in brain structure and function that influence the threshold at which neuropathology clinically manifests, with CR referring more specifically to active adaptation through engagement of task-related or compensatory networks. CR is thus determined by individual differences in cognitive or functional brain processes, which are believed to vary as a function of both innate (i.e., in utero or genetically-determined) and environmental factors.

Of note, as CR exists as a theoretical construct that has not been consistently operationally defined or directly assessed[276], difficulties often arise in its measurement. While Stern and

colleagues[168] proposed that functional neuroimaging approaches may most closely capture the mechanistic underpinnings of CR, CR has been more commonly measured via sociobehavioural proxies that are assumed to covary and contribute to the *development* of CR, such as education, occupational complexity, and cognitive or physical activities. Given that CR research originated in the context of aging or brain injured adults, the most commonly used proxies attempt to capture overall accumulated lifetime enrichment (i.e., educational attainment, word knowledge, IQ). These metrics are, however, less appropriate when examining CR in children and adolescents, as they are inherently tied to age, given that youth have yet to reach their potential in these respects. Moreover, with the impact of neuropathology on brain maturation and the development of crystallized intelligence, measures of IQ are often confounded by the injury itself.

To capture a combination of the protective effects arising from both heritable and environmental factors, we estimated CR using parental education in the current study. In addition to being correlated with intellectual functioning, parental education is tied to other indices of environmental advantage, including advocacy for and uptake of educational and healthcare resources[231, 232, 235, 236, 238, 261, 262], as well as social and parenting behaviours in the home. Parents with higher levels of education have higher expectations for their child's educational attainment and may thus be more likely to prioritize learning-related experiences[236, 237]. Moreover, parental education has been associated with caregiver warmth, which may independently influence cognitive outcomes via reduction of psychosocial stress[236] and help to explain our observed association between higher CR (i.e., parental education) and fewer self-reported symptoms of emotional distress and fatigue.

Importantly, despite its holistic approach to capturing reserves, parental education is limited in being a more remote estimate of CR. It does not directly assess a person's engagement in cognitively-enriching activities, it is fixed for an individual over time, and does not capture how a person may differ from their home environment as they enter young adulthood. While parental education is associated with cognitive outcomes in youth with brain injuries, childhood socioeconomic factors have been poor predictors of cognitive decline in older adults relative to individual achievement, suggesting that accumulated life experiences are important for an individual's cognitive outcome[277]. Moreover, it has been shown that modifiable aspects of reserve (i.e., engagement in cognitive and physical leisure activities) contribute to cognitive outcomes independently from education and occupational experiences[181-183], with stronger effects for individuals with lower education[185]. It thus seems important for estimates of CR to include direct measures of cognitive activities to account for the potential for increased variation from the home environment over time, as well as engagement in activities that are less tied to

socioeconomic position or the individual/family's placement of value on *attainment* in educational or occupational systems. Studies are needed, however, to validate such measures in youth and young adults, as well as to clarify if and how participation in leisure activities varies with age.

Mechanistically, each of these factors are likely to contribute uniquely to the development of reserves. Schwartz and colleagues[182] looked at several contributors to CR in adults with MS (childhood enrichment, occupational attainment, leisure-time cognitive and physical activities), and found low-to-moderate correlations between these metrics, suggesting that these variables represent related but distinct constructs. Heritable factors may influence the inherited risk for learning and other difficulties that may impact baseline cognitive skills[278], as well as natural differences in physiological mechanisms for adaptation[279], or other processes that are important to brain functioning (e.g., vascular health). Physical activity is believed to bolster mechanisms of learning and repair, which may facilitate adaptation to injury as well as the development of reserves[280]. By contrast, engagement in cognitively challenging activities is believed to strengthen and increase the efficiency of networks engaged, while taking part in diverse and dynamic activities likely enhances the flexibility of network recruitment[170, 281]. Importantly, evidence exists to suggest a synergistic association between physical and cognitive activity[282]. Thus, while physical activity enhances plastic mechanisms, cognitive engagement may be necessary for those mechanisms to be utilized toward strengthening relevant networks. Conversely, exposure to family stress may be deleterious to reserves through impacts on the availability of parents, reduced prioritization of cognitive and/or physical activities, as well as through impacts of stress on learning and memory functioning more directly[283]. As such, future research examining CR effects may benefit from measuring this construct comprehensively to more robustly estimate CR.

Composite measures have been utilized in prior research in attempt to summarize across proxies of CR. In one such study, Amato and colleagues[193] created a Z-score composite including education level, premorbid IQ and premorbid leisure activities, and found associations between cortical volume and cognitive performance were moderated by this CR composite in adults with MS. Methods for CR composites need to be further developed to account for common variance between contributors, as well as for potential differences in the weight of their contribution towards the latent factor (i.e., CR). Other approaches may also be considered to estimate contributors toward reserves in youth with MS, such as the Home Observation and Measurement of Environment-Short Form assessment tool[284]. Although not previously used as an estimate for CR, this is a tool for scripted interviewing and home observation that assesses developmentally important parenting interactions and environmental characteristics in a young person's home. While

this measure is more involved than typical metrics of CR and has only been validated for use in youth up to the age of 14, it provides a uniquely direct and holistic measure of social, cognitive and emotional factors that are pertinent to healthy cognitive development. Scores on this measure have been found to mediate relationships between risk factors and cognitive or academic outcomes in youth and young adults[285, 286]. Importantly, studies should take care to concurrently examine the independent associations of these protective factors with cognitive function alongside summary measures to elucidate the nature of their unique contributions to functional outcomes.

5.4 Clinical Implications.

In line with prior research examining neurocognitive functioning in POMS, our results showed specific deficits in working memory, attention/inhibition, visuospatial processing and verbal memory accuracy that existed in addition to, and over and above slowed information processing speed. These findings expand upon current understandings of the neurocognitive profile in POMS to clarify that while slowed processing speed is a common information processing deficit in youth with MS, it is not sufficient to explain other areas of dysfunction. These results thus highlight the breadth of challenges faced by youth with POMS, the need for expansion of cognitive screening beyond measures of processing speed, and the importance of delineating deficits in processing speed and task accuracy in clinical assessment to properly clarify the areas of difficulty experienced by youth with POMS. In turn, these data point to the need for supports that are specific to aspects of cognitive function beyond processing speed. The provision of greater proximity to the teacher, visual cueing, and repetition of instructions, for example, might be helpful in addition to the provision of extra time for learning and testing.

Together with the broader literature, our results provide evidence for domain-specific protective effects of CR in youth with POMS. Most directly, these results help to inform prognostic assessment of POMS patients to consider that not all individuals will fare the same despite similar severity of MS injury, and that those from families with higher education may demonstrate better cognitive performance despite existing neuropathology.

While our proxy for CR (i.e., parental education) is, in itself, tied to socioeconomic position and is not a modifiable factor, CR is not proposed to be as such, but is rather a dynamic construct with heritable, lifestyle and environmental loadings, some of which are associated with socioeconomic factors. In line with prior research tying socioeconomic position to cognitive outcomes in children with brain tumors[272], however, our findings are suggestive of impacts of socioeconomic disparities on outcomes in youth with POMS and point to the need for further research in this area.

Although modifiable contributors to the CR were not directly measured in the present study (e.g., engagement in cognitively or physically enriching activities), there is existing evidence for their impact on cognitive functioning. With consideration of unique challenges that may arise for this population (e.g., accommodations for engagement in physical activity, fatigue), our results encourage the uptake of CR-bolstering activities for youth with POMS as a potential preventative or rehabilitative approach to managing cognitive symptoms. Moreover, our findings point to the need for social supports to reduce disparities in opportunity for cognitively, emotionally and physically enriching environments that may exist between people from different social circumstances.

Given that the construct of CR refers to the latent variable of adaptability, definitions of CR often attempt to capture the impacts of such formative factors holistically. Thus, while evidence for each formative factor speaks to separate mechanisms of protection from cognitive dysfunction, theories of CR align with modern holistic approaches to rehabilitation. Recent advances in rehabilitation are increasingly multifaceted and consider the person as a whole, often incorporating cognitive, emotional and lifestyle components[287]. This follows from an understanding that these factors interact, often synergistically, to influence one's level of functional independence and quality of life. Intervention at one level may thus affect functioning at another. Moreover, current understandings of rehabilitation highlight that interventions are most effective when based on a clients' personal goals and are situated in their life naturalistically to facilitate the relevance and sustainability of the intervention, as well as to build more flexible strategies within a challenging and dynamic real-world context[288, 289]. Evidence for CR effects is thus coherent with this literature and may lend additional support to these approaches to rehabilitation.

Importantly, the CR literature encourages engagement in accessible, non-invasive, and cost-effective approaches to improving functional outcomes. Rather than providing evidence for specific clinical interventions that may require involvement of a specialized health care provider, this literature provides support for lifestyle modifications that are theoretically possible for any person in any setting. While limitations in available time and resources are important considerations for individuals and families in more strained financial and other circumstances, the key message appears to be that engagement in cognitive and physical activities, as well as efforts towards management of stress are beneficial towards one's cognitive functioning. Individuals are thus empowered to engage actively in their own prevention and rehabilitation from cognitive difficulties. Importantly, these messages encourage self-efficacy and resiliency in youth with POMS.

5.5 Limitations and Future Directions

We demonstrated discriminant and construct validity of the PCNB, as well as evidence for protective effects of CR (i.e., parental education) in youth and young adults with POMS. While the PCNB shows some promise for use as a neurocognitive screener, given the breadth of areas which may be assessed with relative ease on a computerized format, further study alongside a full neuropsychological battery is needed to clarify its utility as such. Additional research is also needed to establish its psychometric properties in POMS, including its test-retest reliability and ecological validity[249]. Associations to clinical and functional outcomes, including disability status (e.g., EDSS), MRI markers of disease severity, school functioning and measures of quality of life are necessary to clarify the meaningfulness of these data in the larger context of POMS, and examination of performance on the PCNB longitudinally are important for establishing its utility in tracking disease progression. Similarly, examining CR alongside everyday outcomes will be important to clarify whether reserves not only protect against cognitive symptomatology, but enables functioning more broadly.

Several questions were raised in the current study regarding the role of age at onset in the cognitive profile of POMS. Firstly, our results suggest that processing speed may contribute differentially to the neuropsychological profile in pediatric versus adult-onset MS, however, these relationships were not directly examined. This area of study can be aided through assessment of speed and accuracy of cognitive functioning in individuals with MS along a spectrum of disease onset, as well as with meaningful delineations for critical periods of network development. Similarly, our results raised questions regarding the protection afforded by CR in those with pediatric versus adult-onset MS. Whether such effects actually differ can be illustrated through examination of patients with POMS and adult-onset MS who are matched in disease severity and with consistent methods for measurement of CR and cognitive functioning. Moreover, investigation of these groups over time would help to elucidate whether trajectories of CR exhaustion differ as a consequence of age at disease onset.

As mentioned previously, our study is limited in its measurement of CR. While parental education provides a holistic estimate of heritable aspects of CR and early exposures to cognitive enrichment opportunities, more direct and comprehensive measures of reserve (e.g., including measures of engagement in cognitive and physical activities prior to and following disease onset) would facilitate stronger conclusions regarding the construct. Furthermore, along with these improvements on CR measurement, we posit that CR is best studied with estimates of neuropathology. Given that CR is technically defined not as one's participation in or exposure to enriching activities/environments, but as one's *adaptive capacity*, particularly in the context of brain

injury, this construct cannot be properly assessed without illustrating its moderating role in the relationship between brain injury and functional outcomes. Such moderation effects were examined in a pilot project within the current program of research, however, these findings are excluded from the current discussion due to limitations in our measure of neuropathology. Our measure of MS disease burden was holistically estimated using thalamic volume, given its association with widespread brain injury and robust associations to cognitive outcomes in the literature[46, 47, 97, 102], but failed to meet validation criteria, with limited-to-null correlations with our cognitive outcomes (data not shown).

Of note, this observation highlights limits to the assessment of CR through moderation effects, as discrepancies between one's expected level of cognitive functioning given their degree of injury can also be explained by limitations to chosen measures of neuropathology. While it is perhaps not possible to identify a measure that will precisely capture one's extent of neuropathology to the degree that any discrepancies between it and one's level of cognitive performance can be solely attributable to reserve mechanisms, closer approximations may exist through composite measures that encompass pathology accrued in macro and microstructures of the brain (e.g., capturing lesions, grey matter loss, and damage to normal-appearing white matter). The relevance of the location of brain injury should also be considered as it relates to the cognitive outcome of interest.

5.6 Conclusions

In summary, we found that the PCNB was effective in replicating known patterns of cognitive dysfunction in POMS and provided new insights regarding the independence of cognitive deficits in working memory, attention/inhibition, visuospatial processing, verbal recognition memory and verbal reasoning from slowed processing speed. Different subsets of POMS patients were classified as impaired using the PCNB and SDMT alone, pointing to the need for broader screening to capture patients who are affected cognitively.

Individuals with POMS appear to be afforded some protection by CR, in particular for executive functions (working memory and attention/response inhibition), where patients demonstrated greatest deficit relative to controls and thus a greater need for adaptation to injury. However, while individuals with higher CR showed better cognitive performance overall, it is unclear whether these effects were sufficient to prevent the presentation of deficits relative to their baseline level of functioning.

Further study is needed to understand the clinical utility of the PCNB, as well as to understand how processing speed differentially influences the profile of cognitive dysfunction in

adult-onset versus POMS. Study of CR effects in POMS can be developed with refined measurement of CR, inclusion of MRI measures of disease severity, as well as examination of CR effects as a function of age at MS onset.

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