CEREBELLAR WHITE MATTER MICROSTRUCTURE AND COGNITION IN PEDIATRIC-ONSET MULTIPLE SCLEROSIS

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Abstract

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease that results in neurodegeneration in the central nervous system. The cerebellum is commonly affected in MS and contributes to disease-related impairment. As such, the cerebellum can be studied to provide insights into potential disease mechanisms and treatment in MS. Interest in the functional impact of cerebellar atrophy in MS has increased, as the cerebellum's role in higher-order cognitive processes has been elaborated upon in healthy populations, and cognitive impairment has been widely studied in MS. A gap in the literature exists with respect to exploring how the cerebellum contributes to cognition in pediatric-onset MS. The current study aimed to 1) test whether patients with pediatric-onset MS demonstrate reduced cognitive efficiency compared with healthy age-/sex-matched controls; 2) determine if patients and controls differ with respect to cerebellar volume and microstructural integrity; and 3) determine if patients and controls differ with respect to the association between cerebellar white matter microstructure and cognitive efficiency. Patients demonstrated reduced efficiency on a computerized cognitive battery, relative to healthy controls, most notably on tasks that were timed, or where participants were instructed to respond quickly. Reduced integrity of major cerebellar white matter tracts in patients relative to controls was observed; these findings were driven by patients with pathology in proximity to the cerebellum (i.e., infratentorial lesions). Finally, this study was the first of its kind to provide evidence of a positive association between cerebellar white matter microstructure and cognition in pediatric-onset MS. This relationship was contingent upon infratentorial atrophy. That is, patients with preserved cerebellar microstructure (i.e., without infratentorial lesions) demonstrated a positive association between cerebellar white matter and cognitive efficiency. This association was not present in patients with infratentorial pathology. The current study suggests that MS patients with infratentorial lesions did not demonstrate this association due to disrupted cortico-cerebellar connection (i.e., "network collapse"). We postulate that patients without infratentorial lesions demonstrated this association due to sustained network efficiency due to milder disease burden and intact cortico-cerebellar connectivity. Future research should continue to investigate the structural and functional impacts of this under-studied brain region in pediatric-onset MS.

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Chapter 1: General Introduction

Overview of Multiple Sclerosis

Multiple Sclerosis (MS) is a chronic inflammatory autoimmune disease that results in neurodegeneration in the central nervous system (CNS), with 2-5% of patients diagnosed prior to age 18 (Otallah & Banwell, 2018). More specifically, MS manifests as an autoimmune attack against neurons of the CNS, and is characterized by focal and diffuse lesions (i.e., tissue damage), resulting in atrophy to both white matter (i.e., myelinated axons) as well as grey matter (i.e., the cell bodies and dendrites of the neuron, from which neural impulses originate) (Compston & Coles, 2008; Geurts & Barkhof, 2008). The cause of MS remains largely unknown, but may be attributed to a combination of genetic susceptibility (e.g., family history of MS, genetic haplotypes, single nucleotide polymorphisms) and environmental exposure (e.g., previous infection with Epstein-Barr virus, Vitamin D insufficiency, childhood obesity, smoking/exposure to second-hand smoke) (Banwell et al., 2011; Handel et al., 2010; Harirchian et al., 2018; Marrie, 2004). A latitude gradient of MS incidence has been observed, such that countries further from the equator demonstrate higher rates of MS, which may in part explain the relationship between Vitamin D insufficiency and increased MS risk (Wallin et al., 2019). Migration studies suggest MS as secondary to environmental exposure. That is, adult migrants retain the risk of MS from their country of origin, whereas children born to migrants assume the risk of the country migrated to (Dobson & Giovannoni, 2019). Biological sex has been widely noted as another risk factor contributing to MS susceptibility, with a female to male sex ratio of 3 to 1 (Orton et al., 2006). Interestingly, this sex difference appears only in post-pubertal MS patients, suggesting a role of gonadal hormones in MS susceptibility (Huppke et al., 2014).

MS can be classified into 3 major subtypes, including relapsing remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS). Relapsing-remitting MS is the most common clinical presentation, and is characterized by alternating periods of remission (i.e., relative clinical stability without the accrual of new neurological symptoms) followed by relapse (i.e., the emergence of new symptoms, or the worsening of existing symptoms) (Klineova & Lublin, 2018). As the disease progresses, the frequency of acute inflammatory activity diminishes. Disability accumulates with the continuous worsening of neurological symptoms over at least 6 – 12 months, leading to a secondary progressive disease course. The median time to conversion to SPMS is approximately 19 years following the onset of RRMS (Rovaris et al., 2006). Finally, PPMS is observed in approximately 10-20% of patients, and is characterized by ongoing progression of neurological symptoms from disease onset, without the initial relapsing-remitting presentation (Klineova & Lublin, 2018)

Clinical presentation of MS at onset commonly includes visual (e.g., double vision, visual loss), sensory (e.g., numbness, tingling), muscular (e.g., spasticity, weakness, gait difficulties, pain), and proprioceptive (e.g., dizziness, vertigo) symptoms (Compston & Coles, 2008). Neurological disability is measured using the Expanded Disability Status Scale (EDSS), which quantifies physical disability on a 10-point scale (i.e., 0 = no disability; 10 = death due to MS). Fatigue is another hallmark symptom contributing to reduced quality of life in MS, and affecting up to 83% of adult patients (Manjaly et al., 2019). Psychiatric symptoms such as depression and anxiety also impact approximately 30-50% and 22% of adult MS patients, respectively, further contributing to reduced quality of life in this population (Boeschoten et al., 2017; Feinstein, 2011). There is currently no cure for MS, warranting endeavours to better understand the consequences of the illness, in an effort to inform rehabilitation strategies and treatment.

Pediatric-Onset Multiple Sclerosis

Disease onset of MS typically occurs in adulthood, between the ages of 20 and 40 years (Chiaravalloti & DeLuca, 2008). However, onset prior to 18 years of age represents approximately 2-5% of all MS cases (Banwell et al., 2007; Otallah & Banwell, 2018; Waldman et al., 2014; E. Ann Yeh et al., 2009). The median age of first attack in pediatric-onset MS is typically between the ages of 11 and 13 years (Otallah & Banwell, 2018). Pediatric-onset MS presents largely as a relapsing-remitting disease (Otallah & Banwell, 2018; Yeh et al., 2009), with the annualized relapse rates highest in the first two years post-incident attack, and some research demonstrating higher relapse rates in the pediatric population compared to adult MS patients (Banwell et al., 2007; Gorman, Healy, Polgar-Turcsanyi, & Chitnis, 2009). Moreover, longitudinal research has noted that children with MS continue to demonstrate elevated relapse rates compared to adults, following 6-year follow-up (Chitnis, 2013). As noted, progressive subtypes of MS also exist in adults, with severity of disability accumulating over time. In children, however, progressive subtypes are very rare, with fewer than 3% of patients with pediatric-onset MS showing this presentation.

Noteworthy differences exist between adult and pediatric-onset MS with regards to brain morphology characteristics, as measured by magnetic resonance imaging (MRI). When matched to adults with similar disease duration, pediatric-onset MS patients demonstrate higher T2-weighted lesion volume, and greater tissue injury (Yeh et al., 2009). However, in spite of greater lesion accrual, pediatric-onset patients demonstrate slower physical disability accrual (as measured by the Expanded Disability Status Scale; EDSS) (Chitnis, 2013) and a longer median time to reach severe disability (20 years post-onset, compared to 10 years post-onset in adult

MS) (Renoux et al., 2007). Early in the disease course, physical disability typically remains low in pediatric-onset MS (i.e., EDSS score below 3)(Otallah & Banwell, 2018).

Multiple Sclerosis and the Developing Brain

In contrast to adults with MS, who already have mature and established neural networks at the time of disease onset, inflammation and demyelination resulting from pediatric-onset MS occur as neural networks are actively developing (Portaccio et al., 2010). Pediatric-onset MS poses a significant risk to normal brain maturation, given that the brain continues to undergo development well into young adulthood (Lebel & Beaulieu, 2011). As such, there has been an increase in the application of advanced MRI techniques to better understand the impact of pediatric-onset MS on the developing brain.

MRI studies have observed declines in age-expected brain growth among pediatric-onset MS patients (Aubert-Broche et al., 2014), along with whole brain atrophy (Kerbrat et al., 2012), relative to age-matched healthy children. The neurodegenerative features of MS may even precede the first clinical attack, as one study noted that pediatric MS patients demonstrated lower brain volume than controls at the time of diagnosis (Kerbrat et al., 2012). The thalamus has been regarded as a brain region particularly vulnerable to MS disease pathology. Failure of age-expected thalamic growth has also been noted in this patient population, as well as loss of thalamic volume with disease progression; findings that are more prominent in patients with higher total brain T2-weighted lesion load (Aubert-Broche et al., 2014). In addition to grey matter atrophy, decreased white matter integrity is consistently observed in pediatric-onset MS patients, relative to healthy controls (Akbar, Giorgio, et al., 2016; Blaschek et al., 2013), and correlates with longer disease duration (Blaschek et al., 2013). Studies have also noted impaired age-expected growth in normal appearing white matter, as well as progressive loss of tissue

integrity over time in MS patients (Longoni et al., 2017). Sex differences in white matter growth trajectories have also been noted in pediatric-onset MS, with females exhibiting greater declines in white matter integrity relative to males (Longoni et al., 2017). As such, pediatric-onset MS may have a milder impact on normal appearing white matter development in males, which may be attributed to sex-differences in neuroanatomical properties (e.g., males exhibit thicker axons and more rapid radial growth relative to females; Perrin et al., 2009; Pesaresi et al., 2015).

Cerebellar Atrophy in Multiple Sclerosis

The brain can be divided into the supratentorial area (containing the cerebrum, choroid plexus, pineal gland, hypothalamus, pituitary gland, and optic nerve) and the infratentorial area/posterior fossa (containing the cerebellum, tectum, and brain stem). Pediatric-onset MS patients present with greater infratentorial lesion involvement (i.e., volume and quantity), relative to adult-onset MS patients matched for disease duration (Ghassemi et al., 2014; Waubant et al., 2009). Infratentorial lesions are common in pediatric-onset MS, and observed in up to 75% of patients (Ghassemi et al., 2014).

The cerebellum is commonly affected in MS and can be studied to provide insights into potential disease mechanisms and treatment (Wilkins, 2017). In a recent consensus paper, experts agreed that cerebellar atrophy contributes considerably to disease-related impairment in MS, particularly in progressive subtypes (Weier et al., 2015), and interest in the impact of cerebellar atrophy on MS disease pathology has steadily increased over the last decade. This region is of particular interest, as MS disease pathology is associated with cerebellar damage and extensive cerebellar demyelination (Kutzelnigg et al., 2007). However, research on the functional impact of cerebellar atrophy in MS is still in its infancy and remains a subject matter to be further investigated.

Functionally, the cerebellum is divided into cortico-cerebellar circuits that integrate sensory-motor and cognitive-behavioural networks (Weier et al., 2015). As such, MS-related damage to the cerebellum may have a diffuse effect on a variety of brain functions, contributing to disability. Cerebellar symptoms (i.e., tremor, nystagmus, and ataxia) were once considered a common feature of MS (Poser & Brinar, 2001), and are now known to represent the predominant clinical manifestation in up to one-third of patients (Rot et al., 2008). However, whether atrophy in the cerebellum has functional and clinically meaningful consequences in MS remains a matter of study.

MRI studies have confirmed extensive atrophy to the cerebellum in both relapsing-remitting and progressive MS subtypes (Anderson et al., 2009; Calabrese et al., 2010). This has been reflected by the revised McDonald criteria for the diagnosis of MS, which recognizes infratentorial lesions as a common site of atrophy (Polman et al., 2011; Thompson et al., 2018). Studies have shown significant reductions in cerebellar grey matter in adult MS patients compared to healthy controls (Anderson et al., 2009; Calabrese et al., 2010; Weier, Penner, et al., 2014), as well as reductions in white matter volume (Weier, Penner, et al., 2014). Longitudinal studies of adult MS have noted that involvement of the cerebellum at disease onset is associated with a more aggressive disease course (i.e., shorter time to severe physical disability and earlier onset of progressive disease) (Novotna et al., 2015; Weinshenker et al., 1991).

More specifically, T2 hypointensities (i.e., lesions) have been noted in the dentate nuclei of the cerebellum in patients with MS (Tjoa et al., 2005) which has been suggested to reflect non-heme iron deposition related to MS pathology (Weier et al., 2015). Notably, other studies have observed T2 hypointensities within the dentate nuclei in the context of normal aging (Maschke et al., 2004). T1 hypointensities in the dentate nuclei of the cerebellum have only been

noted in the context of MS pathology, although this was predominantly observed in the progressive subtype (Roccatagliata et al., 2009).

Cerebellar white matter lesions have been well-described in adult patients with MS, with lesions in the cerebellar peduncles commonly noted, as well as in the dentate and olivary nuclei (Weier et al., 2015; Wilkins, 2017). In cases of progressive MS, cerebellar cortical demyelination appears to be more prevalent than in relapsing-remitting MS, with one study reporting, on average, 38.7% of the cerebellar cortex affected in a cohort of SPMS and PPMS patients, compared to sparse cerebellar cortical demyelination in RRMS patients (0 - 7.5%) (Kutzelnigg et al., 2007). With respect to cerebellar white matter, in a cohort of MS patients with various phenotypes, the majority of patients presented with T2 lesions in the middle cerebellar peduncle (65% of patients), and nearly half demonstrated T2 lesions in the superior peduncles (43% of patients) (Preziosa et al., 2014). These findings were related to increased clinical disability, with more abnormal white matter integrity of the peduncles associated with ambulatory impairment.

MS-related reductions in white matter microstructure, as measured by diffusion tensor imaging (DTI), have been noted in the cerebellar peduncles, which are the major white matter tracts connecting the cerebellum with the cerebrum (Anderson et al., 2011; Moroso et al., 2017). These reductions have also been associated with increased clinical disability, such as impairment in upper limb function and walking (Anderson et al., 2011), as well as balance impairment (Prosperini et al., 2013).

In addition to the impact on cerebellar anatomy, studies have noted functional connectivity changes in the cerebellum as a result of MS. For instance, some studies have observed reduced cerebellar functional connectivity (e.g., in left lobules V and VI) in MS patients, relative to healthy controls (Dogonowski et al., 2014). In addition, reductions in intra-

cerebellar functional connectivity, between the left Crus I and the dentate nuclei, was more pronounced in patients with higher physical disability. This study also noted that increased lesion load of the left cerebellar peduncle was associated with decreases in cerebellar functional connectivity, highlighting the direct impact of cerebellar pathology on brain function.

A handful of studies exist that have examined functional impairment in relation to disruption of cerebellar functional connectivity in adult MS patients. For instance, Saini et al. (2003) noted that MS patients demonstrated reduced cerebellar-premotor cortex functional connectivity relative to controls during a figure drawing task, while groups did not differ with respect to task performance. In addition, another study noted functional connectivity changes between prefrontal areas and the cerebellum during an inhibition (i.e., Stroop) task that was dependent on MS phenotype (Rocca et al., 2012). That is, patients with RRMS demonstrated increased recruitment of the cerebellum and other regions of interest (i.e., frontal and parietal lobes), while patients with SPMS demonstrated a nonspecific pattern of neural activation. The authors postulate these results reflect over-exhaustion of brain areas with disease progression in MS. This hypothesis was further supported by the observation that shorter disease duration correlated with increased right cerebellar activity. In both the MS and control groups, faster response time in the incongruent Stroop condition correlated with increased cerebellar activity; however, greater cerebellar recruitment was noted in the MS group. Nevertheless, the MS group demonstrated slower response time relative to healthy controls, as well as a higher percentage of errors, highlighting the need for increased neural resources, or functional reorganization, in MS. Finally, Loitfelder et al. (2012) noted that better performance on a processing speed task was associated with increased functional connectivity between the anterior cingulate cortex (ACC) and the cerebellum in MS patients. In healthy controls, processing speed performance did not

associate with cerebellar-ACC functional connectivity, suggesting possible functional reorganization in the MS group.

It has been suggested that disruption to cerebellar functional connectivity may reflect temporal-spatial disintegration of cortico-cerebellar and spino-cerebellar inputs, as a result of MS lesions in cerebellar white matter (Weier et al., 2015). Although MS-related changes in functional connectivity of the cerebellum may vary across studies, these findings demonstrate that disruption to cortico-cerebellar networks can trigger functional changes in the cerebellum. Longitudinal studies are required to determine if these changes are a result of cerebellar dysfunction, or due to compensation, in light of tissue atrophy.

Less is known with respect to cerebellar involvement in pediatric-onset MS; however, an increasing amount of research has been published in this regard over the last decade. Notably, cerebellar dysfunction, including ataxia and nystagmus are observed in 5-27% of pediatric-onset MS patients, and ataxia has been noted in approximately 50% of patients with MS onset prior to 10 years of age (Banwell et al., 2007; Gorman et al., 2009; Huppke et al., 2014). Greater incidence and number of T2-weighted lesions in the posterior fossa (i.e., the brainstem and cerebellum) have been noted in pediatric-onset MS patients, compared to adults matched for disease duration (Ghassemi et al., 2014; Waubant et al., 2009). This finding has been primarily observed in the cerebellar peduncles and cerebellar white matter. Recent studies have noted altered cortical-cerebellar connectivity in pediatric-onset MS, particularly in cognitively impaired patients (Cirillo et al., 2016), as with adult MS (Moroso et al., 2017). Others have observed decreased functional connectivity in the cerebellar lobule VI and vermis in pediatric-onset MS patients compared to age- and sex-matched controls (Rocca et al., 2014).

Finally, one study reported impaired age-expected growth of the cerebellum in pediatric MS patients (Weier et al., 2015). Over a mean follow-up period of approximately 3 years, both patients and controls demonstrated an inverted U-shaped growth trajectory for total cerebellar volume, as well as cerebellar grey and white matter volumes. Patient growth curves peaked earlier relative to healthy controls (12-14.5 vs. 14 years in girls; 14-16 vs. 17 years in boys), indicating a failure of maximal age-expected growth. Moreover, decline in cerebellar volume was noted earlier and more pronounced in patients compared to healthy controls. Independent of diagnostic group, growth curves of the cerebellum peaked earlier in girls than for boys. Interestingly, neither supra- nor infratentorial lesion volume had a significant effect on cerebellar volumes, and the presence of infratentorial lesions at first scan did not predict cerebellar growth rate or final volume. When cerebellar subregions were examined, posterior lobe trajectories appeared to demonstrate marked reductions in volume compared to healthy controls, while the anterior lobes did not. Overall, this study confirmed that MS onset during childhood and adolescence poses a significant negative impact on age-expected growth of the cerebellum.

In summary, cerebellar atrophy plays an important role in both adult and pediatric-onset MS. However, few cross-sectional studies to date have specifically examined how cerebellar atrophy impacts functional outcomes (i.e., cognition) in pediatric-onset MS. While the cerebellum has been long understood as one of the first regions of the brain to develop and become myelinated (Barkovich et al., 1988), recent studies in healthy children and adolescents have demonstrated that the cerebellar peduncles continue to mature in adolescence (Simmonds et al., 2014). As such, acute inflammatory insult to cerebellar networks that are actively developing renders them vulnerable and may impact the development of processes that rely on cerebellar activity, such as cognition.

The Cerebellum and Cognition

The cerebellum has long been regarded as a brain structure implicated in motor control, namely balance and coordination (Blumenfeld, 2010). This structure has been shown to have similar organization as the cerebral cortex, with primary and secondary somatosensory areas (Henneman, Cooke, & Snider, 1952), specifically in the anterior lobes. Notably, most of the cerebellar posterior lobes have no body-representation or connection to the primary motor areas of the cerebral cortex (Schmahmann, 2019). Studies have noted connections between the posterior regions of the cerebellum and cortical regions responsible for cognitive and emotional functioning (Allen & Tsukahara, 1974; MacLean, 1949). As such, a more in-depth examination of the cerebellum's role in higher-order cognitive processes has been elaborated upon in recent research.

Topographically precise regions of the cerebellum are intimately linked with the cerebral cortex through feed-forward (the corticopontine-pontocerebellar projection) and feedback loops (cerebello-thalamocortical projection). The former connects the motor cortex to the cerebellar anterior lobes (including lobules I through V and parts of lobule VI and VIII) via feed-forward projections through the pontine nuclei, whereas feedback from the cerebellar nuclei to the motor cortex occurs through the thalamus (Kelly & Strick, 2003; Thach, 1987). These anterior regions of the cerebellum also receive afferents from the inferior olivary complex, which receives input from the spinal cord (Brodal, 1981; Voogd, 2004). As such, the role of the anterior region of the cerebellum in motor control is evident, based on its intimate circuitry with spinal afferents and sensorimotor areas of the cortex.

In contrast, the posterior portion of the cerebellum (i.e., the remainder of lobule VI, lobule VIIA/B, Crus I/II, lobule IX) has no connections with the motor cortex and no spinal cord

inputs (Brodal, 1981; Voogd, 2004). Rather, this region of the cerebellum is linked to association areas of the cerebral cortex that are responsible for higher-order processes, including the prefrontal cortex, posterior parietal cortex, superior temporal regions, cingulate gyrus, and posterior hippocampal area (Kelly & Strick, 2003; Schmahmann, 1991, 1996; Schmahmann & Pandya, 1997). Efferents from the cerebellar posterior regions originate in the dentate nucleus of the cerebellum and link to the cerebral association areas via the thalamocortical and corticopontine feedforward/feedback projections. **Figure 1** illustrates the projections outlined above.

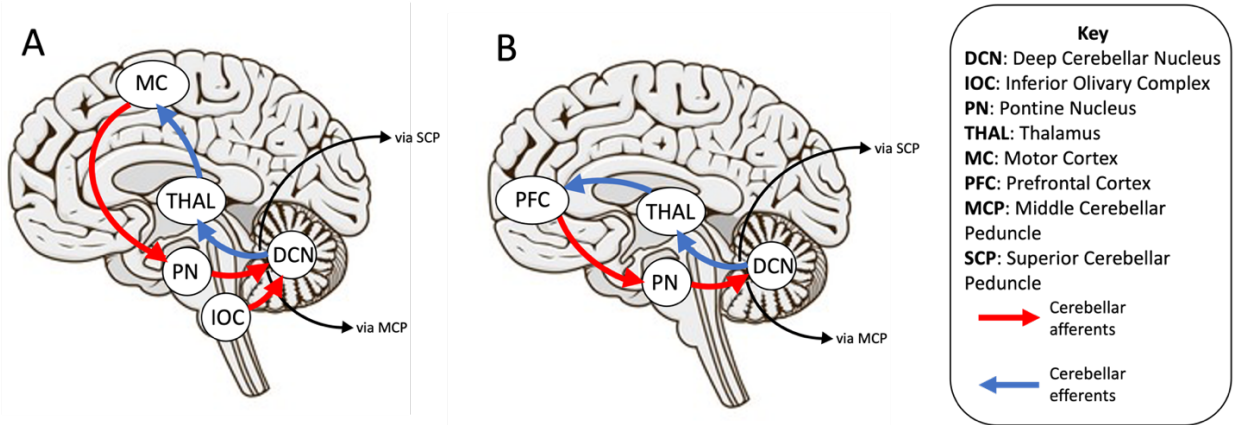

Figure 1. Illustration of the cerebellothalamocortical (blue) and corticopontocerebellar (red) projections from the anterior (A) and posterior (B) cerebellum. Cerebellar efferents exit the cerebellum via the superior cerebellar peduncle (SCP); cerebellar afferents enter the cerebellum via the middle cerebellar peduncle (MCP). A) The anterior cerebellum projects to the motor cortex (MC). B) The posterior cerebellum projects to cerebral association areas, such as the prefrontal cortex (PFC). Figure adapted from Fernandez et al. (2018).

In summary, the cerebellum appears to have dichotomous connections with the cerebral cortex, such that the sensorimotor projections are noted in anterior cerebellar regions, while cognitive projections are found in the posterior cerebellum. Circuitry with the anterior cerebellum appears to be integral for motor control, while circuitry with the posterior cerebellum is necessary for neural processing that subserves cognition and emotion (Schmahmann, 2019).

Stroke patients with lesions localized to the anterior, or "motor," region of the cerebellum demonstrate symptoms of cerebellar motor syndrome, including dysmetria, dysarthria, and ataxia (Manto et al., 2012). In contrast, posterior cerebellar lesions in the "cognitive" region of the cerebellum can result in "cerebellar cognitive affective syndrome," which has been characterized by executive dysfunction and other cognitive deficits (Schmahmann, 2019). More recently, functional domains of the cerebellum have been established specific to language, spatial and emotional processing, as well as social cognition (Schmahmann, 2019).

The first organizational map of cerebellar functional networks was published by Buckner et al. (2011) using resting-state functional connectivity data from 1000 subjects. Their findings demonstrated that most of the cerebellum mapped to cerebral association networks, including those involved in sensorimotor integration, cognitive control, and the default mode network. Subsequent work supported these findings using task-based functional MRI, noting that cerebellar regions that are coupled with the cortical dorsal attention network (i.e., cerebellar lobules VIIb/VIIIa) were activated during attention and working memory tasks, and cerebellar regions coupled with the cortical default-mode network were suppressed (Brissenden et al., 2016).

In addition, the percentage of the cerebellum dedicated to a network has been predicted by the size of the network in the cortex (Buckner et al., 2011). A more recent resting-state functional connectivity study noted that the frontoparietal network, which is thought to support adaptive control, was observed to have a 2.3-fold greater representation in the cerebellum, relative to the cortex (Marek et al., 2018). This study also noted that network-specific cerebellar blood-oxygen level dependent (BOLD) signals temporally lagged cortical BOLD signals,

suggesting that, for each functional network represented in both the cortex and cerebellum, the cerebellum represents the "final destination" for signals propagating from the cortex.

There is substantive evidence for the role of the cerebellum in a wide range of nervous system functions, beyond traditional views of a limited contribution to sensorimotor functioning. The cerebellum's complex role in cognition has been conceptualized as the "dysmetria of thought theory." That is, while damage to the anterior cerebellum results in limb dysmetria, damage to the posterior cerebellum results in dysmetria of thought. This theory notes that, much like the cerebellum is responsible for regulating the rhythm, rate, force, and accuracy of movements, it is also responsible for regulating the speed, consistency, and appropriateness of cognitive processes (Schmahmann, 1991). Notably, the cerebellum is not responsible for these cognitive processes, per se, but rather *regulates* such processes. The cerebellum achieves this through integrating diverse streams of information from the cortex, and optimizes cognitive performance according to context (Schmahmann, 2019). A recent consensus paper has highlighted this view, citing the role of the cerebellum in experience-driven adaptive control (Caligiore et al., 2017). Moreover, the modulatory role of the cerebellum on cortical network functioning has been demonstrated in healthy adults following transcranial magnetic stimulation of the cerebellar midline, leading to increases in corticocortical functional connectivity of the dorsal attention network (Halko et al., 2014).

Given the role of the cerebellum in cognition, as well as its involvement in MS pathology, a more in-depth examination of its role in cognitive processing in MS has been investigated in recent research.

Cognitive Impairment in Pediatric-Onset Multiple Sclerosis

According to the existing literature, MS diagnosed in childhood/adolescence appears to have a detrimental impact on regional and global brain development, affecting both white and grey matter. Ultimately, the harmful impact that MS poses to maturing neural networks has the potential to disrupt many brain functions, particularly cognition.

Cognitive impairment occurs in approximately one-third of pediatric-onset MS patients, with both the prevalence and severity of impairment increasing with disease progression (Amato et al., 2010; Banwell & Anderson, 2005; MacAllister et al., 2005). Cognitive deficits have been observed in a number of domains, including attention, processing speed, visuomotor integration, working memory, episodic memory, visuospatial ability, and more often than in adults, verbal abilities (e.g., expressive and receptive language) (Amato et al., 2008; Amato et al., 2014; B. L. Banwell & Anderson, 2005; Cardoso et al., 2015; MacAllister et al., 2005; Till et al., 2013; Till, Ghassemi, et al., 2011). Less consensus exists with regard to the impact of MS on cognitive flexibility, planning, and non-verbal problem-solving. Longitudinal research to examine the long-term consequences of pediatric-onset MS on cognitive functioning is limited; however, among the studies that exist, reductions in cognitive abilities over time, or a failure to acquire age-expected developmental gains, have been noted (Amato et al., 2014; Amato et al., 2010; Hosseini et al., 2014; MacAllister et al., 2007; Till et al., 2013). Disruption to cognitive functioning in children and adolescents has consequences on academic achievement and quality of life, making prevention or remediation of cognitive dysfunction a critical goal of research in this field.

The Cerebellum and Cognition in Multiple Sclerosis

The cognitive profile of patients with MS and cerebellar involvement remains a topic of debate in the field. Cerebellar lesions are a common feature of adult MS, and studies have demonstrated that patients with cerebellar motor syndrome show more severe cognitive deficits compared to patients without, particularly with respect to processing speed and word association tasks (Valentino et al., 2009; Weier et al., 2014). Cognitive impairment in MS patients with cerebellar involvement may be due to damage in cortical-cerebellar loops. Indeed, one study noted reduced functional connectivity between the left cerebellar Crus I and the right superior parietal lobule during a working memory task in MS patients with cerebellar atrophy (Cerasa et al., 2012). Another observed correlations with grey matter loss in the cerebellum and dorsolateral prefrontal cortex and impairment in executive function in MS (Weier, Penner, et al., 2014). In addition, studies have also noted correlations between atrophy of the superior temporal cortex and cerebellum with language performance (Cerasa et al., 2013). Consistent with these findings, a recent study demonstrated that lower anterior cerebellar volume predicted poorer motor performance, and that lower posterior cerebellar lobe volume predicted worse working memory and processing speed in MS patients relative to healthy controls (D'Ambrosio et al., 2017).

In general, injury to the cerebellum has been associated with impairment in a wide range of cognitive domains, including verbal fluency, working memory, attention, and executive function (Tedesco et al., 2011). Interestingly, in adult onset MS, patients with cerebellar lesions demonstrate a different cognitive profile than those without cerebellar involvement (Weier et al., 2014). That is, total cerebellar volume was lowest in patients showing the highest degree of cognitive disability, in contrast to patients without cerebellar atrophy. In addition, one study demonstrated that cognitively impaired patients with relapsing-remitting MS had a higher

proclivity of lesions in the middle cerebellar peduncle, which was associated with cognitive dysfunction (Tobyne et al., 2018).

In MS patients with cerebellar signs, total cerebellar volume explained 26% of the variance in processing speed, as measured by the Symbol Digits Modalities Test (SDMT), and 23% of the variance on the Paced Auditory Serial Addition Task (PASAT) (Weier, Penner, et al., 2014). However, this variance was also largely explained by overall brain atrophy (i.e., normalized brain volume and whole brain T2 lesion volume). Patients with cerebellar atrophy also demonstrated higher fatigue scores than patients without cerebellar involvement. More recent research has confirmed these findings, noting an association between reductions in cerebellar posterior lobe volume and impaired processing speed in MS patients, (Cocozza et al., 2017; Moroso et al., 2017), and that cerebellar posterior lobe volume (i.e., lobules VI, Crus I, and VIIIa) predicts visual spatial processing and verbal memory performance (Cocozza et al., 2017). One study noted that posterior cerebellar volume uniquely contributed 13.1% of the variance in fine motor dexterity, 5.6% in processing speed performance, 4.3% in visual spatial memory, and 5.5% in verbal working memory (Cocozza et al., 2017).

Some studies have observed that lower white matter integrity in the cerebellar peduncles was associated with impaired cognitive functioning (Hulst et al., 2013; Mesaros, et al., 2012; Yu et al., 2012), reduced working memory, and slower processing speed (Moroso et al., 2017). Notably, cerebellar white matter *microstructure* in adult MS has shown greater predictive utility on cognitive outcomes compared to cerebellar posterior lobe *volume* (Moroso et al., 2017).

Task-based functional MRI studies have also been conducted to examine the functional impact of MS pathology on cerebellar activity. For instance, diminished cerebellar activity has been noted in MS patients during working memory tasks, which may in part explain the working

memory impairment that is commonly observed in MS (Li et al., 2004). In contrast, higher cortico-cerebellar functional connectivity has been associated with greater information processing speed performance in both cognitively impaired and cognitive preserved MS patients (Pasqua et al., 2021; Savini et al., 2019). These studies suggest that altered cerebellar activity may contribute to disrupted cognitive performance.

Nevertheless, the contribution of cerebellar pathology on cognitive outcomes in pediatric-onset MS has yet to be fully elucidated. Given that pediatric patients have higher infratentorial lesion volume compared to their adult counterparts, the study of how MS-onset in childhood impacts cerebellar function is of particular interest. Moreover, pediatric-onset MS patients show a higher lesion burden in the cerebellar peduncles and cerebellar white matter compared to adult-onset MS patients matched for disease duration. One study demonstrated that cerebellar posterior lobe volume predicted processing speed and vocabulary in pediatric onset MS patients, but not in age- and sex-matched healthy controls (Weier et al., 2016). It was also noted that total cerebellar volume and infratentorial volume accounted for the additional variance in vocabulary and processing speed tasks. Interestingly, cerebellar volume did not differ between patients and healthy controls. Beyond this study, the effect of insult/atrophy to the cerebellum on cognitive dysfunction in pediatric-onset MS remains to be investigated. Given the evidence of demyelination present in the posterior fossa in this patient population, the impact of the cerebellum on cognitive functioning in pediatric-onset MS should be further explored.

Study Objectives and Hypotheses

Objectives: The current study aimed to: 1) Test whether patients with pediatric-onset MS show reduced cognitive efficiency compared with healthy age-/sex-matched controls; 2) Determine if patients and controls differ with respect to cerebellar volume and microstructural

integrity; and 3) Determine if patients and controls differ with respect to associations between cerebellar white matter microstructure and cognitive efficiency. An exploratory aim was to investigate how results differ between patients with infratentorial lesions present and absent.

Hypothesis 1: Cognitive efficiency, as measured by the Penn Computerized Neurocognitive Battery, was hypothesized to be reduced in pediatric-onset MS patients compared to healthy controls, most notably on tasks that have greater time constraints.

Hypothesis 2: Pediatric MS patients were hypothesized to show reduced cerebellar volume, as well as reduced white matter cerebellar microstructure, relative to controls. Volume reductions were predicted to be more pronounced in the posterior cerebellum, relative to the anterior cerebellum, as noted in previous literature. Microstructural abnormalities were predicted in the cerebellar peduncles, the major white matter tracts that provide afferents to and efferents from the cerebellum. Reductions in volume and microstructure were expected to be greater in patients with infratentorial lesions, relative to patients without infratentorial lesions.

Hypothesis 3: Cerebellar white matter microstructure was expected to associate with cognitive efficiency more strongly in MS patients compared to healthy controls. The cerebellar peduncles were hypothesized to demonstrate stronger associations in MS patients with more significant disease pathology (i.e., greater total T2 lesion volume and infratentorial lesions present).

Student Contributions to Project

E. De Somma was involved in cognitive data collection in Toronto, ON (i.e., administering the Penn Computerized Neurocognitive Battery to patients and healthy controls), as well as in quality control of cerebellar segmentation and image registration. All statistical analyses and study conceptualization was also conducted by E. De Somma. MRI processing was

computed by collaborators at the Montreal Neurological Institute and the Children's Hospital of Philadelphia.

Chapter 2: Cognitive Efficiency in Pediatric-Onset MS vs. Healthy Controls

It has been postulated that cognitive performance is governed by a limited set of processing resources, such as cognitive efficiency (i.e., the efficiency with which cognitive operations are performed accurately) (Rypma et al., 2006; Vernon, 1983). Some theorists have noted that measures of cognitive efficiency, such as processing speed, are fundamental to cognitive development, as these measures are consistently related to indices of higher-order cognition, including fluid intelligence and short-term memory (Kail & Salthouse, 1994). That is, theories of cognitive efficiency suggest that cognitive performance is *maximized* when cognitive operations are performed quickly, and when neural resources are *minimized* for such operations (Rypma et al., 2006). Developmentally, non-linear age-related improvements in performance have been observed in response time across a variety of cognitive tasks, such as mental rotation and picture matching (Kail, 1986), as well as visual/memory search, mental addition, and figural matrices tasks (Kail, 1988). Some longitudinal work has noted a quadratic function for the developmental change in processing speed, such that a steep increase in processing ability is noted during early and middle childhood, which begins to slow in late childhood and early adolescence, and which finally begins to plateau in late adolescence (Kail & Ferrer, 2007).

Proposed mechanisms to explain this rate of change have suggested that the quantity of "processing resources" available increases with development. These resources may refer to age-related changes in neural communication, such as developmental increases in neural connectivity (Khundrakpam et al., 2016) and myelination (Oyefiade et al., 2018; Schmithorst et al., 2002; Schmithorst & Yuan, 2010). For instance, prior research has noted associations between age-related improvements in processing speed and prefrontal cortex maturation/connectivity (Rypma et al., 2006). As such neural resources increase, an individual's cognitive efficiency improves

and predicts developmental improvement on cognitive task performance (e.g., working memory, inductive reasoning, arithmetic) (Kail, 1991). Accordingly, it has been suggested that individual differences in intelligence can be moderately attributed to the variance in the speed/efficiency with which individuals execute cognitive operations (Kail, 1986; Kail & Salthouse, 1994). Indeed, cognitive processing efficiency is fundamental to abilities such as reasoning, problem-solving, and memory.

Reduction in processing speed is the most commonly observed deficit in both pediatric and adult MS (Banwell & Anderson, 2005; Bergendal et al., 2007; Bethune et al., 2011; Deluca et al., 2004; Denney et al., 2004; Till et al., 2013; Till, Deotto, et al., 2011; Till, Ghassemi, et al., 2011; Yeh et al., 2009). Moreover, processing speed deficits have been consistently shown to be sensitive to MS-related pathology (Denney et al., 2004; Till, Ghassemi, et al., 2011). In pediatric-onset MS, clinically-meaningful decline (i.e., a decrease in z-score of 1.0 or greater) in processing-speed performance was observed in 14% of patients after a mean follow-up period of 1.8 years (Wallach et al., 2020), showing that decline can occur in the early stages of the disease. In a one-year follow-up study, pediatric-onset MS patients failed to show age-related improvements in processing speed, compared to age- and sex-matched healthy controls (Till et al., 2013). In another longitudinal study, processing speed performance yielded 77% sensitivity and 81% specificity for predicting cognitive impairment in MS patients following more extensive neuropsychological testing after one year (Charvet, Beekman, et al., 2014). In a more recent prospective study examining pediatric acquired demyelinating syndromes (ADS), clinically significant declines in processing speed and working memory were noted in 19 – 42% of patients, 2 years post-ADS onset (De Somma et al., 2021). In addition, some studies have noted that, after adjusting for age, adult patients with a history of pediatric-onset MS are at

greater risk of cognitive impairment and processing speed impairment, relative to patients with adult-onset MS (McKay et al., 2019; Ruano et al., 2018). Moreover, processing speed in pediatric-onset MS patients declines at a faster rate than in adult-onset patients (McKay et al., 2019).

In adult MS patients, processing speed declines have been associated with reduced cognitive performance in other domains, including memory, learning, and attention (Chiaravalloti et al., 2013; Genova et al., 2012; Leavitt et al., 2011). However, when controlling for processing speed, some studies have noted that differences between MS patients and healthy controls on tasks of working memory (Leavitt et al., 2011), response inhibition (Denney & Lynch, 2009), planning (Owens et al., 2013), task switching (Leavitt et al., 2014), and attention (Roth et al., 2015), were no longer present. These findings highlight the impact that processing speed contributes to other higher-order cognitive domains, as theorized in developmental research (Kail & Salthouse, 1994). Indeed, when MS patients are asked to perform a task more quickly, they are pushed to their processing capacity and generally perform more poorly.

A speed-accuracy trade-off occurs when a person sacrifices accuracy on a task in order to perform more quickly, and vice versa (Katsimpokis et al., 2020). An example of speed-accuracy trade-off in MS is described in Owens et al. (2013), who noted that performance on the Tower of London task only differed between patients and healthy controls when time was constrained (i.e., no differences in performance were noted when groups performed the untimed task). As such, authors concluded that deficits in planning are a consequence of MS-related deficits in information processing speed. Consistent with this work, Leavitt et al. (2014) did not observe group differences on executive tasks without processing speed demands (i.e., Wisconsin Card Sorting Task), while performance on executive tasks with time constraints was reduced in the

MS group (i.e., Stroop Task, Trail Making Test). Indeed, studies have highlighted that a deficit in speed (vs. accuracy) is the primary information-processing deficit in MS (Lengenfelder et al., 2006). In other words, a speed-accuracy trade-off may be quite relevant to this group.

A large body of literature has been dedicated to addressing speed-accuracy trade-offs in cognitive performance measurement (Liesefeld et al., 2015; Liesefeld & Janczyk, 2019; Vandierendonck, 2017). The speed-accuracy trade-off can be manipulated in behavioural tasks through a variety of methods, including altering verbal instructions (i.e., instructing participants to prioritize accuracy over speed, or vice versa), and response deadlines (i.e., timed tasks) (Heitz, 2014). For example, Katsimpokis et al. (2020) manipulated speed-accuracy trade-offs on a series of visual perception tasks by altering speed and accuracy cues, as well as trial deadlines. They noted faster response times on trials with deadlines and speed cues, and observed accuracy improvements on trials without deadlines and with accuracy cues. As such, the authors concluded that the speed-accuracy trade-off can be manipulated according to the experimental conditions.

In order to account for speed-accuracy trade-offs in experimental data, several methods for combining accuracy and response time into a single performance measure have been proposed (Liesefeld & Janczyk, 2019; Vandierendonck, 2017). In a study evaluating the utility of different speed-accuracy integration procedures, the *balanced integration score (BIS)* was observed as the most useful combined measure to remove speed-accuracy trade-off effects (i.e., (Liesefeld et al., 2015; Liesefeld & Janczyk, 2019). This measure is calculated by bringing mean response time and mean accuracy (i.e., percent correct) scores to the same scale through z-score standardization, followed by subtracting one standardized score from the other (Liesefeld et al., 2015). As such, accuracy and response time are given equal weights:

$$BIS_{i,j} = z_{PC_{i,j}} - z_{RT_{i,j}}$$

$$\text{with} \quad z_{x_{i,j}} = \frac{x_{i,j} - \bar{x}}{SD_x}$$

Liesefeld & Janczyk (2019) note many advantages to using combined measures of speed and accuracy. Importantly, in using a measure such as BIS, the analysis is protected from spurious effects due to speed-accuracy trade-offs. Moreover, creating a combined measure of response time and accuracy increases statistical power, in cases where participants focus more on speed, or on accuracy in their responding. Finally, the authors note that using the BIS method is of particular utility when testing *relative performance* (i.e., if one group performs better relative to a comparison group), as the score is based on the sample mean and standard deviation.

Using a combined speed/accuracy score such as the BIS is useful when examining performance data from computerized test batteries, on which both response time and accuracy are recorded. The BIS method has been utilized to combine speed and accuracy scores on the Penn Computerized Neurocognitive Battery (PCNB); a one-hour battery designed to measure a variety of neurobehavioural domains (Gur et al., 2010, 2012; Moore et al., 2015). A recent study from our group noted that pediatric-onset MS patients demonstrated reduced accuracy on several PCNB tasks (i.e., working memory, attention/inhibition, verbal memory, and visuospatial processing tasks), after adjusting for response time as a covariate (Barlow-Krelina et al., 2021). Reductions in overall response time on the PCNB were also noted in pediatric-onset MS patients, relative to healthy controls. Given that the BIS method increases power by combining speed and accuracy, it is possible that generating a combined score on the PCNB may be more sensitive to detect group differences in performance between pediatric-onset MS patients and healthy controls, than examining accuracy and response time independently.

Study One

Reduced cognitive efficiency, as measured by processing speed tasks, has been consistently observed in pediatric-onset MS patients, in addition to impairments observed in other cognitive domains. As noted in adult MS samples, impaired cognitive performance may be a function of a heightened speed-accuracy trade-off (i.e., diminished processing capacity). Examining measures of cognitive functioning that integrate accuracy and processing speed will help to further characterize cognitive functioning in pediatric-onset MS. The purpose of Study One was to extend upon the work of Barlow-Krelina et al. (2021) and compare a *combined* speed and accuracy score (i.e., cognitive efficiency measured by the BIS) on the PCNB between patients with pediatric-onset MS and healthy age- and sex-matched controls. It was hypothesized that patients would demonstrate reduced cognitive efficiency relative to controls.

Methods

Participants

Participants in the MS group of the current study were part of the Canadian Pediatric Demyelinating Disease Study (CPDDS) (Verhey et al., 2011). The CPDDS includes sites from across Canada as well as the Children's Hospital of Philadelphia (CHOP) in the United States. Enrollment of CPDDS participants between August 2015 and June 2019 included youth aged less than 18 years who consented within 180 days of disease onset. Patients with incident MS were recruited consecutively from MS outpatient clinics using advertising (i.e., flyers, letters to residents and staff physicians, and web advertisement). Healthy controls were recruited in Toronto (The Hospital for Sick Children) and Philadelphia (CHOP) via community advertising (i.e., flyers, web). The current study sample included patients aged 8 to 27 years (including participants who had been followed since < 18 years of age). Patients were classified as having pediatric-onset MS, per the 2017 McDonald Diagnostic Criteria (Thompson et al., 2018).

Patients with monophasic demyelination, MOG-related demyelination, anti-AQP4-related neuromyelitis optica spectrum disorder, or non-demyelinating disease were excluded from the present study. Written and informed consent/assent was obtained from all participants, or a parent/legal guardian.

Between 2015 and 2019, all English-speaking participants enrolled in the CPDDS (104 MS participants and 139 healthy controls) were offered neurocognitive testing. Neurocognitive data were obtained for 70 (67.3%) of MS participants and 109 (78.4%) of healthy controls. One healthy control participant was excluded due to familiarity with the assessment battery; two MS participants were excluded due to insufficient visual/motor ability to perform cognitive testing. A final sample of 68 pediatric-onset MS and 108 healthy controls was included in the analytic dataset for the current study. Neurocognitive data were obtained from eight sites, including seven tertiary health care centres across Canada and one site in the U.S. (**Supplemental Table 1**).

Measures

Demographic and clinical measures

Demographic characteristics, developmental milestones, education and occupation, and relevant medical history (i.e., date of MS onset, disease duration at time of cognitive testing, number of relapses) were recorded for each participant using standardized study case report forms. Physical disability in MS participants was measured by study site neurologists (more than 91 days following a physician-approved episode) using the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). Emotional distress (i.e., symptoms of depression and anxiety) was measured using the Paediatric Index of Emotional Distress (PI-ED) (O'Connor et al., 2016) for participants under 16 years of age, and using the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) for participants age 16 and older. Scores on the PI-ED range from 0-

42, with a score greater than 20 indicating clinically significant emotional distress (O'Connor et al., 2016); scores on the HADS range from 0-21, with a score greater than 10 in the clinical range (Zigmond & Snaith, 1983). The PedsQL Multidimensional Fatigue Scale was used to measure self- and proxy- (e.g., parent) reported fatigue; scores on this measure range from 0-100, with higher scores reflecting fewer fatigue-related problems (Varni & Limbers, 2009). Socioeconomic status was measured by the Barratt Simplified Measure of Social Status, which uses total education and occupation for both parents/guardians to yield a score between 8-66 (Barratt, 2005). Participants also reported the number of years of education completed by themselves and by each parent; parental education values were averaged to obtain a total score.

Cognitive Evaluation

Cognitive performance was evaluated with the children's version of the Penn Computerized Neurocognitive Battery (PCNB) (Gur et al., 2010). This is a fully automated computerized battery, comprising cognitive tests that have been validated in a population-based sample of 9428 youth, aged 8-21 years, and has been shown to have a high sensitivity for detecting cognitive impairment in youth with different neuropsychiatric conditions (Gur et al., 2012). The PCNB includes 14 tests (described in detail in Table 1), which assess: abstraction and flexibility, working memory, attention, episodic memory (i.e., face, object, and word memory), verbal and non-verbal reasoning, spatial reasoning, emotion recognition, emotion and age differentiation, and sensorimotor function (i.e., finger tapping speed, motor praxis). Each of the 14 measures on the PCNB yields an accuracy score and an average response time for correct items (with the exception of the two sensorimotor tasks, which only provide response time scores).

Table 1. Description of neurocognitive tasks of the Penn Computerized Neurocognitive Battery

Subtest	Neurobehavioural function	Test Description

Short Letter N-Back	working memory, shifting	Sequence of uppercase letters displayed; participants instructed to respond according to condition: 0-back: respond to "X"; 1-back: respond if letter is identical to preceding letter; 2-back: respond if letter is identical to letter 2 trials back
Go-No-Go Task	inhibitory control, sustained attention	Respond to target based on letter and location on screen
Penn Conditional Exclusion Test	cognitive flexibility, rule learning, working memory	Decide which object does not belong in an array of four objects; according to three changing sorting principles
Penn Face Memory Test	facial recognition	Identify which faces were seen in a previous study list (20 target faces, 20 foils); determined based on Likert scale (definitely yes/no, probably yes/no)
Penn Word Memory Test	verbal recognition	Identify which words were seen in a previous study list (20 target words, 20 foils); determined based on Likert scale (definitely yes/no, probably yes/no)
Short Visual Object Learning Test	object recognition	Identify which figures were seen in a previous study list (20 target figures, 20 foils); determined based on Likert scale (definitely yes/no, probably yes/no)
Short Penn Verbal Reasoning Test for Children	verbal reasoning	Select from a list the word that best completes a verbal analogy
Penn Matrix Analysis Test	nonverbal reasoning	Choose the geometric piece that best completes a matrix
Variable Short Penn Line Orientation Test	spatial ability, visual discrimination	Rotate a line until it is parallel to a fixed line, with as few clicks as possible
Age Differentiation Task	age differentiation	Identify which of the two faces is older
Penn Emotion Recognition Test for Children	emotion identification	Identify the emotion displayed on a face from a list of emotions (happy, sad, anger, fear, neutral)
Measured Emotion Differentiation Task	emotion differentiation	Identify which of two faces is displaying a more intense expression
Finger Tapping Test	motor speed	Tap on the spacebar as quickly as possible for 10 seconds with the index finger; alternates between dominant and nondominant hand
Motor Praxis Task	sensorimotor processing speed	Move the mouse and click a green square that moves to different locations on the screen and becomes smaller

Each cognitive evaluation was administered by a trained assessor during a single session and took approximately one hour to administer on a laptop computer. Task order was consistent across participants and included breaks at three standard intervals throughout the assessment, in order to maintain engagement and prevent fatigue(Gur et al., 2012).

Cognitive data were examined for quality control in detail via assessor administration comments regarding behavioural and environmental observations pertinent to testing (e.g., presence of distractions, misunderstanding instructions, low motivation, fatigue). Invalid data from the PCNB administration were excluded from analyses.

Analysis

Generating standardized scores

Percentage correct (i.e., accuracy score) was derived for each subtest by dividing the number of correct trials by the number of total trials on each task and multiplying by 100. Response time scores referred to the average response time for the correct items on each task. Percent correct and response time scores for each PCNB outcome were standardized into Z-scores using the means and standard deviations (SD) of the HC group (N=108). Consistent with Moore et al. (2015), response time z-scores were transformed (i.e., multiplied by -1), such that higher response time z-scores could be interpreted as better performance (i.e., faster response time). Extreme scores were Winsorized to 3 standard deviations from the mean (Field, 2016).

An “efficiency score” was computed for each task by adding the Winsorized accuracy and response time z-scores. This method is mathematically equivalent to the BIS method, as our response time z-scores are multiplied by -1 prior to computing the efficiency score. A proof illustrating the equivalence of these methods is detailed in **Appendix A**.

By using an efficiency score, speed of processing is incorporated into all outcomes, such that a participant with an accuracy z-score of 2.50 (very accurate) and a response time z-score of -2.50 (very slow) would produce an efficiency score of 0. This method of computation for deriving an efficiency score has been utilized with the PCNB in previous studies (Moore et al., 2015), and as previously noted, has been shown to be a more stable method for comparing groups on performance, when accounting for speed-accuracy trade-offs (Liesefeld & Janczyk, 2019). Efficiency scores were computed for all tasks on the PCNB (11 in total) with the exception of the sensorimotor tasks (i.e., no accuracy score) and the Penn Conditional Exclusion Test. The latter was excluded from the efficiency analysis, as errors in this task are indicative of not yet knowing the categorization rule. As suggested by Vandierendonk (2017), more elaborate processing occurs following an error, as the participant is signalled to change the currently applied categorization rule. Consequently, it is suggested that speed and accuracy relate to different processes in this task. That is, an increased response time on this task will not necessarily result in a decrease in accuracy, but may interfere with the processes required for selecting a new categorization rule. In this task, integrating speed and accuracy would not provide a more stable measure of performance, thus, an efficiency score was not calculated (Vandierendonck, 2017).

A composite efficiency score was computed by averaging PCNB subtest efficiency scores (11 tasks). The developers of the PCNB noted that the efficiency scores had acceptable fit in a confirmatory factor analysis assessing a 4-factor structure of the PCNB (i.e., executive functioning, complex cognition, episodic memory, and social cognition) in a healthy sample of children and youth aged 8-21 years (*N*=9,138) (Moore et al., 2015). In the current study, domain scores were not computed, as a confirmatory factor analysis revealed that the model fit was

unacceptable for the efficiency scores in our sample of MS participants (Rubenstein, unpublished).

Statistical Analysis

Between group differences for clinical and demographic variables were computed using Welch's t-test or chi-squared (X^2) tests, where appropriate. Mann-Whitney U tests were computed for variables which did not meet the assumption of normality (according to visualization of histograms and Shapiro-Wilk's test of normality). Effect sizes for the between-group comparisons of clinical and demographic data were determined using Cohen's *d*. An alpha threshold of $p \leq .05$ was applied for demographic comparisons between groups.

Between-group differences for PCNB efficiency outcomes were computed using multiple linear regression with group as a predictor. The model was adjusted for age and age^2, as scatterplots revealed a quadratic function of age for each efficiency score (see **Supplemental Figure 1**). Additional covariates included sex, as well as parental education. Notably, parental education and socioeconomic status were moderately correlated ($r = 0.59$, $p < .001$); parental education was selected as a covariate to remain consistent with previous studies publishing on this sample and the PCNB (Barlow-Krelina et al., 2021), and due to missing SES data.

Associations between PCNB efficiency z-scores and clinical variables in the MS group were computed using multiple linear regression, with age and age^2 included in the model, as cognitive outcomes were not age-normed and the model was improved with inclusion of a quadratic age term. Only efficiency scores which differed between groups were examined for clinical associations.

All models were tested for meeting linear regression assumptions, including normality (Shapiro-Wilk's test and histograms/Q-Q plots), homoscedasticity (Studentized Breusch-Pagan

test and plot of residuals vs. predicted values), and linearity (plot of residuals vs. fitted values). Outliers were identified by examining Cook's Distance plots and running sensitivity analyses on potential outlying datapoints. Outliers were removed if they had significant influence on the model. An alpha threshold of $p \leq .01$ was applied for between group comparisons of PCNB outcomes and clinical associations, to adjust for multiple comparisons and guard against false positive findings.

Results

Clinical and demographic results

Clinical and demographic data of the MS and healthy control (HC) groups are presented in Table 2. No statistical group differences were observed with respect to age, sex, participant level of education, or emotional distress. The MS group was found to have higher self- and parent-rated fatigue ($p < .001$), lower socioeconomic status ($p = .03$), and lower parental education ($p = .009$) relative to the HC group.

Table 2. Demographic and clinical characteristics of MS and HC participants

Clinical/Demographic Variable	*n*	MS	*n*	HC	*p*	Cohen's *d*
Age at testing (years; mean, range)	68	18.3(8-27)	108	17.0(8-29)	.074	0.27
Sex (female:male, %female)	68	49:19 (72.1)	108	74:34 (68.5)	.74	-
Participant education (years)	68	11.6(3.4)	108	11.1(4.2)	.46	0.11
Parental education	66	14.3(2.0)	99	15.1(2.3)	**.009**	0.41
Socioeconomic status	36	36.0(15.7)	70	43.0(15.1)	**.03**	0.45
Emotional Distress (#normal:high, %high)	54	32:22(40.7)	86	59:27(31.4)	.34	-
Participant Fatigue (median; range)						
Parent-rated	63	63.9(1.4-100)	80	88.9(45.8-100)	**<.001**	0.9
Participant-rated	66	62.5(26.4-98.6)	98	74.31(13.9-100)	**.002**	0.56
Age at disease onset (years; median,range)	68	15.3(6.3-17.9)	-	-	-	-
Disease Duration (months; median, range)	68	19.4(0.8-134)	-	-	-	-
EDSS (median, range)	68	1.5(0-3.5)	-	-	-	-
DMT (#Y, %yes)	68	56(82.3)	-	-	-	-

Number of clinical attacks (median; range)	68	1(1-11)	-	-	-	-

Abbreviations: MS = multiple sclerosis; HC = healthy control; EDSS = Expanded Disability Status Scale; DMT = Disease Modifying Therapy
Note: Values indicate *mean(SD)*, unless otherwise indicated. Values in bold are significant at $p \leq .05$.

Between-group differences in PCNB efficiency

Results of the multiple regression examining group differences on efficiency z-scores are presented in **Table 3**. Relative to healthy controls, MS participants demonstrated lower efficiency z-scores on four subtests, including the Go-No-Go (-0.24 vs. 0.02, $p = .002$), Line Orientation (-0.60 vs. 0.04, $p < .001$), Verbal Memory (-0.63 vs. 0.04, $p = .001$), and Face Memory (-0.56 vs. 0.01, $p = .005$). The PCNB Composite score was also lower in the MS group, relative to controls (-0.31 vs. 0.00, $p < .001$). Accuracy and response time z-scores are also presented in Table 3.

Table 3. Results of multiple regression demonstrating unstandardized beta coefficients for group status (i.e., MS vs. HC) on efficiency z-scores on the Penn Computerized Neurocognitive Battery.

Test (z-score)	n	MS M(*SD*)	n	HC M(*SD*)	B(SE)	*p*	95% CI
N-back							
Efficiency	63	-0.23(1.73)	97	0.02(1.46)	-0.45(0.23)	.05	-0.91 to 0.0004
Accuracy		-0.35(1.02)		0.02(0.93)	-0.45(0.14)	**.002**	-0.73 to -0.17
Response time		0.12(1.07)		0.01(0.97)	-0.006(0.16)	.97	-0.33 to 0.32
Go-No-Go							
Efficiency	66	-0.24(1.45)	99	0.02(1.49)	-0.56(0.18)	**.002**	-0.92 to -0.20
Accuracy		-0.11(0.97)		0.02(0.94)	-0.28(0.12)	.02	-0.52 to -0.04
Response time		-0.13(1.11)		0.01(0.98)	-0.24(0.15)	.11	-0.55 to 0.06
Verbal Reasoning							
Efficiency	62	-0.06(1.48)	96	-0.05(1.21)	-0.07(0.22)	.77	-0.50 to 0.37
Accuracy		-0.22(1.18)		0.005(0.98)	-0.30(0.16)	.05	-0.61 to 0.004
Response time		0.10(0.78)		0.01(0.96)	0.04(0.14)	.78	-0.23 to 0.32
Matrix Analysis							
Efficiency	66	-0.22(0.65)	99	0.01(0.67)	-0.25(0.11)	.02	-0.46 to -0.04
Accuracy		-0.14(0.98)		0.00(1.00)	-0.11(0.16)	.50	-0.42 to 0.19
Response time[a]		-0.08(1.01)		0.01(0.97)	-0.10(0.15)	.50	-0.41 to 0.20
Line Orientation							
Efficiency	66	-0.60(1.33)	97	0.04(1.35)	-0.73(0.21)	**<.001**	-1.14 to -0.32

Accuracy		-0.23(0.87)		0.00(1.00)	-0.30(0.14)	.04	-0.58 to -0.01
Response time		-0.37(1.06)		0.01(0.97)	-0.39(0.16)	.02	-0.71 to -0.06
Verbal Memory							
Efficiency	66	-0.63(1.64)	98	0.04(1.56)	-0.77(0.24)	**.001**	-1.24 to -0.30
Accuracy		-0.32(0.91)		0.02(0.95)	-0.39(0.14)	**.006**	-0.67 to -0.11
Response time		-0.31(1.10)		0.02(0.91)	-0.38(0.15)	.011	-0.67 to -0.09
Face Memory							
Efficiency	66	-0.56(1.72)	97	0.01(1.51)	-0.70(0.25)	**.005**	-1.19 to -0.21
Accuracy		-0.24(1.03)		0.00(1.00)	-0.24(0.17)	.15	-0.56 to 0.90
Response time		-0.32(1.22)		0.01(0.97)	-0.46(0.17)	**<.001**	-0.80 to -0.13
Object Memory							
Efficiency	65	-0.26(1.52)	98	0.01(1.33)	-0.38(0.21)	.08	-0.80 to 0.04
Accuracy[a]		-0.21(1.18)		0.00(1.00)	-0.18(0.18)	.32	-0.52 to 0.17
Response time		-0.05(0.90)		0.01(0.95)	-0.16(0.14)	.24	-0.44 to 0.11
Age Differentiation							
Efficiency	66	-0.27(1.59)	99	0.01(1.57)	-0.35(0.25)	.16	-0.84 to 0.14
Accuracy		0.03(0.92)		0.01(0.98)	-0.05(0.15)	.75	-0.34 to 0.24
Response time[a]		-0.30(1.22)		0.00(0.99)	-0.24(0.18)	.17	-0.59 to 0.11
Emotion Recognition							
Efficiency	65	-0.16(0.27)	98	0.06(1.45)	-0.23(0.21)	.28	-0.65 to 0.19
Accuracy		0.20(0.69)		0.02(0.97)	0.17(0.14)	.22	-0.10 to 0.45
Response time		-0.36(1.19)		0.04(0.91)	-0.40(0.16)	.012	-0.71 to -0.09
Emotion Differentiation							
Efficiency	66	-0.08(1.23)	99	0.00(1.41)	-0.22(0.21)	.29	-0.63 to 0.19
Accuracy		0.01(0.84)		0.00(1.00)	-0.15(0.14)	.30	-0.43 to 0.13
Response time[a]		-0.09(1.14)		0.00(1.00)	-0.03(0.17)	.86	-0.36 to 0.30
PCNB Composite							
Efficiency	66	-0.31(0.82)	99	0.00(0.86)	-0.43(0.11)	**<.001**	-0.65 to -0.22
Accuracy		-0.15(0.54)		0.00(0.61)	-0.21(0.08)	**<.001**	-0.37 to -0.06
Response time		-0.17(0.67)		0.00(0.58)	-0.23(0.09)	**.01**	-0.42 to -0.05

[1]Unstandardized beta coefficients for predictor "group".
Model adjusted for age, I(age^2), sex, parental education, with the exception of models with superscipt[a] which were adjusted for age only where plots indicated a non-quadratic relationship with age. Parental education was included in the model, and data were available for 99 HCs and 66 MS. Values in bold are significant at $p \leq .01$. Sample size differs across tests due to exclusion of invalid subtest data.

Clinical correlates of PCNB efficiency scores

Clinical associations were examined with PCNB efficiency outcomes that differed between groups. Older age at onset was associated with greater efficiency on the Go-No-Go task

(B = 0.23, p = .01), and higher number of clinical attacks was associated with lower efficiency on the Line Orientation task (B = -0.33, p < .001). Notably, neither of these associations remained statistically significant when disease duration was added to the model. Additional associations that were observed at a threshold of $p \leq .05$ are noted in **Table 4.**

Table 4. Clinical associations with PCNB efficiency outcomes in the MS group.

Clinical variable	Efficiency Score	B(SE)	*p*	95% CI
Disease duration (yr)	Go-No-Go	-0.02(0.008)	.02	-0.03 to -0.004
Age at onset (yr)	Go-No-Go	0.23(0.09)	**.01**	0.05 to 0.41
Number of episodes	Line Orientation	-0.33(0.12)	**.008**	-0.56 to -0.09
	PCNB Composite	-0.13(0.06)	.03	-0.25 to -0.01
EDSS	*n.s.*			
Emotional distress	*n.s.*			
Fatigue	*n.s.*			

Note: Model adjusted for age, I(age^2). Values in bold are significant at $p \leq .01$. *n.s.* = non-significant associations

Discussion

In Study One, cognitive functioning was examined in pediatric-onset MS patients using cognitive efficiency scores derived from the PCNB computerized battery. Notably, pediatric-onset MS participants had lower efficiency scores relative to healthy controls on tasks of inhibition/attention (i.e., Go-No-Go), spatial ability (i.e., line orientation), and recognition memory (i.e., verbal memory, face memory), as well as the PCNB composite score. Results (Table 3) suggest that, on some tasks (i.e., Go-No-Go, Line Orientation), efficiency scores may be more sensitive to detecting between-group differences relative to examining response time or accuracy scores independently.

Reduced efficiency on the Go-No-Go task is consistent with previous research noting reduced performance on tasks of inhibition/attention in pediatric-onset MS patients (Banwell & Anderson, 2005; Till et al., 2011). Notably, on the Go-No-Go task, fixed response time intervals

are set (i.e., up to 2.5 seconds). Therefore, adjusting for a speed-accuracy trade-off is relevant for patients who may compromise accuracy to respond within the time limit. Indeed, upon examining accuracy and response time scores on this task, the MS group did not statistically differ from healthy controls with respect to response time; however, reduced accuracy scores approached statistical significance. As such, our efficiency analysis provided the necessary power to detect the group difference in performance, and highlights the impact that time constraints have on tasks of inhibition and attention in this patient group. Notably, while the efficiency score for the Go-No-Go task was sensitive to group differences, efficiency score reductions on the time-constrained working memory task (N-back task) only approached statistical significance ($p = .05$). On this working memory task, MS patients were less efficient than healthy controls (i.e., MS patients exhibit lower working memory efficiency by 0.45 SD units, relative to controls). Follow-up analyses indicated that accuracy was reduced on this task in the MS group ($p = .002$), whereas response time was not ($p = .97$). Similar to the Go-No-Go task, MS participants' accuracy was limited by the time constraint on the N-back task. As observed in healthy individuals (Heitz & Engle, 2007) and in adults with MS (Leavitt et al., 2011), working memory impairment may be reflective of reduced processing speed capacity. Previous work in adult-onset MS has noted that deficits in working memory are no longer present when processing time is increased (Leavitt et al., 2011). Moreover, theories of cognitive development have noted that processing speed abilities contribute to working memory capacity (Fry & Hale, 2000; Kail & Salthouse, 1994). In general, combining accuracy and response time z-scores adjusts for a speed-accuracy trade-off, particularly on time-constrained tasks; however, the results above illustrate the importance of examining how speed and accuracy contribute to the efficiency score.

On the visual perception task (Line Orientation), combining speed and accuracy into an efficiency score provided the necessary power to detect a group difference, as reduced accuracy and response time in the MS group both approached statistical significance, relative to healthy controls. When scores were combined, statistically significant lower efficiency scores were observed in the MS participants. This is consistent with previous work that has observed reduced visuoperceptual (Barlow-Krelina et al., 2021; Till, Ghassemi, et al., 2011) and spatial recall performance (De Meo, Portaccio, et al., 2021) in patients with pediatric-onset MS, relative to healthy controls.

In contrast, we did not find a statistically significant group difference in cognitive efficiency on the PCNB Verbal Reasoning task. This finding is inconsistent with past research that has noted reductions in Verbal IQ and language processing abilities among pediatric-onset MS patients (Amato et al., 2010; Till, Ghassemi, et al., 2011; Till et al., 2013). Our results may suggest that this specific computerized verbal reasoning task is not sensitive to MS-related impairment, as participants are asked to select a word from a list, rather than generate a word independently. Notably, 18% of MS participants (12/64) and 19% of healthy controls (22/106) received a perfect score on this task. As such, this verbal reasoning task may have been too easy to detect a group difference in our sample of youth. Consistent with prior work, no statistically significant group differences in efficiency were detected on a perceptual reasoning task (Matrix Reasoning) (Akbar et al., 2016; Barlow-Krelina, 2021; Till et al., 2011). However, in the current study, group differences approached statistical significance (B = -0.25, p = .02), suggesting poorer perceptual reasoning efficiency in the MS group. Despite there being no statistically significant difference, it is plausible that accuracy on these tasks requires additional processing resources in patients with MS. This has been suggested by functional neuroimaging research that

has observed increased cortical activation on processing speed and executive control tasks in pediatric-onset MS patients, despite there being no group differences in task accuracy (Barlow-Krelina et al., 2019), or response time (Akbar, Banwell, et al., 2016). As such, individuals with MS may be compensating for disease pathology by recruiting greater neural resources in order to maintain speed and performance.

Consistent with prior knowledge regarding verbal episodic memory in pediatric-onset MS (Amato et al., 2010; Barlow-Krelina et al., 2021; De Meo et al., 2021), statistically significant reductions in Verbal Memory efficiency scores were observed in the current study. Unsurprisingly, this effect appeared to be driven by both reduced accuracy and response time in the MS group, relative to healthy controls. Notably, the episodic memory tasks of the PCNB do not have a time constraint, allowing participants an open window to respond. It appears that, despite taking more time to respond, accuracy on the Verbal Memory task was reduced in the MS group, providing further evidence for verbal memory difficulties in this patient population. Similarly, lower efficiency scores were noted on the Face Memory task in the MS group. Upon examination of accuracy and response time z-scores, individuals in the MS group performed this task significantly more slowly than healthy controls, and thus were able to maintain task accuracy (albeit, the effect size suggests relatively poorer accuracy in the MS group; B = -0.24). These findings provide further support for the impact of slowed information processing speed on cognitive performance in pediatric-onset MS.

MS participants did not statistically differ from healthy controls on the Social Cognition tasks of the PCNB (i.e., age differentiation, emotion recognition, and emotion differentiation). Findings in adult MS samples are mixed with respect to emotion processing deficits (Cotter et al., 2016; Pinto et al., 2012). Reduced emotion processing has been noted in pediatric-onset MS

on higher-order emotion processing, such as theory of mind tasks (Charvet, Cleary, et al., 2014). As such, the tasks in the current study may not have been appropriate to detect group differences which have been for more advanced emotion processing skills in previous research.

Younger age at onset was associated with worse performance on the Go-No-Go task; however, in the current sample, younger age at onset was also associated with longer disease duration ($r = -0.40$). As such, it is difficult to disentangle the effects of younger age from disease duration (which was also associated with worse performance on the Go-No-Go task). Nevertheless, previous research has noted poorer long-term cognitive outcomes in patients with younger age at MS onset (Hosseini et al., 2014; Till et al., 2012). At a younger age, fewer major white matter tracts are fully myelinated (Barnea-Goraly, 2005). As such, the CNS may be more vulnerable to inflammation and limited in its capacity to reorganize neural networks for cognitive processing. In addition, increased disease burden, as measured by a greater number of clinical attacks, was associated with lower efficiency scores on the Line Orientation task. This adds to recent literature which has noted an association between impaired processing speed and a higher number of relapses prior to cognitive testing (Wallach et al., 2020). However, in the current study, this association was also no longer statistically significant when controlling for disease duration. Thus, longer disease duration appears to account for the association between cognitive efficiency and younger age at onset, as well as relapse rate.

Summary of Study One findings

Given the well-documented deficits in processing speed noted in MS, it is unsurprising that patients demonstrate reduced performance on tasks that are either timed, or where they are instructed to respond quickly. In Study One, efficiency scores (a combined speed/accuracy measure) were examined on a computerized cognitive battery to investigate the speed-accuracy

trade-offs that may contribute to impaired cognitive performance in pediatric-onset MS. Patients demonstrated reduced cognitive efficiency on four tasks of the PCNB. Generally speaking, this study demonstrated that using an efficiency score accounts for the impact of cognitive processing speed on task performance. However, in one instance (i.e., N-back task), accuracy was more sensitive than efficiency in detecting a group difference. As such, it remains important to interpret efficiency scores within the context of accuracy and response time.

Research in adult-onset MS has previously noted that processing speed deficits may account for impaired cognitive functioning, and that when task demands for speed are eliminated, cognitive processing is unimpaired. In pediatric-onset MS, processing speed impairment has been widely studied. The current findings add to this literature and highlight the need to account for processing difficulties in pediatric-onset MS. As processing speed is a supportive cognitive process that mediates other domains of functioning (e.g., academic achievement, socialization) (Charvet, Beekman, et al., 2014; Till, Deotto, et al., 2011), access to educational supports are important for this patient population, to ensure that such children and youth reach their maximum potential.

To extend upon these findings, neural predictors of cognitive efficiency in this sample of pediatric-onset MS patients will be explored in Study Three. Specifically, the cerebellum will be examined, as it has been hypothesized that the disruption to cortico-cerebellar pathways may lead to poorer cognitive performance, given the cerebellum's role in regulating cognitive processes and supporting automation (Savini et al., 2019).

Chapter 3: Cerebellar Volumetric and Diffusion Properties in Pediatric-Onset MS vs. Healthy Controls

The cerebellum is commonly affected in MS, demonstrating significant demyelination (Kutzelnigg et al., 2007), increased T2 lesion load (Anderson et al., 2009), as well as reduced grey and white matter volumes relative to healthy controls (Calabrese et al., 2010). As such, studying this brain region is important for developing further insights with respect to MS disease mechanisms and pathology, as well as biomarkers for evaluating treatment efficacy (Wilkins, 2017). Diffusion tensor imaging is a non-invasive method that can be utilized to characterize microstructural integrity of neural tissue. A small body of literature has examined cerebellar atrophy in MS as measured via diffusion tensor imaging and will be elaborated upon in this chapter.

What is diffusion tensor imaging?

Diffusion tensor imaging (DTI) is a neuroimaging method which utilizes water diffusion in the brain to quantify the degree of tissue integrity (Soares et al., 2013). Two general measures arise from DTI: 1) the degree of tissue anisotropy, and 2) the degree of water diffusion through the tissue. Anisotropy refers to the directionality of water diffusion (Soares et al., 2013). High anisotropy indicates that the diffusion of water is more directionally constrained and linear, such as water movement through a straw. Isotropy refers to water diffusion that is uninhibited and uniform in all directions, much like the movement of water in a glass (Ranzenberger & Snyder, 2020). Depending on the tissue type, structure, and integrity, water will diffuse differently in the brain. For example, in cerebral spinal fluid (CSF), water diffusion is unrestricted (i.e., isotropic) (Soares et al., 2013). In grey matter, diffusion is more anisotropic compared to CSF, as cell membranes and tissue structure slow the rate of diffusion (Feldman et al., 2010; Soares et al.,

2013). In white matter, axons are enveloped by a myelin sheath (a fatty insulating layer that facilitates signal propagation). As such, the rate of diffusion perpendicular to axon fibres is hindered and restricted along the axon, making water diffusion directionally-dependent and highly anisotropic (Feldman et al., 2010; Soares et al., 2013). Fractional anisotropy (FA) is the most widely used DTI measure and reflects the degree of anisotropy in a given region of interest. Notably, FA is a dimensionless measure with values that range from 0 when diffusion is completely isotropic, to 1 when diffusion is completely anisotropic (Van Hecke et al., 2016).

The second parameter acquired from diffusion tensor imaging is the degree of water diffusion. This metric is divided into three measures: mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) (Soares et al., 2013). MD refers to the overall diffusion of water, regardless of its direction, and is an aggregate of RD and AD. RD refers to diffusion perpendicular to the principal direction (i.e., the direction of greatest diffusion), whereas AD refers to diffusion parallel to the principal direction (Soares et al., 2013).

Making meaning of DTI metrics

FA is an indirect marker of white matter integrity, such that higher anisotropy reflects more directionally-restricted diffusion, and thus, healthier tissue (Tae, 2018). FA has also been noted as the most sensitive metric for detecting change in microstructure; however, it is unspecific to the cause of decreases in anisotropy (Ranzenberger & Snyder, 2020). As such, diffusivity metrics are increasingly reported in DTI studies. That is, RD reflects myelin neuropathology and increases with demyelination, whereas AD reflects axonal degeneration and increases with axon loss and brain maturation (i.e., pruning) (Le Bihan et al., 2001). In patients with MS, FA is typically reduced relative to healthy controls and MD increased, which has been noted to reflect diminished white matter integrity and myelin content in pathological studies

(Kolasinski et al., 2012; Sbardella et al., 2013b). Similar findings have also been noted in DTI studies of MS that have examined group differences in normal appearing white matter (NAWM; i.e., white matter with lesions excluded) (Bammer et al., 2000; Cercignani et al., 2000; Filippi, 2001; Filippi et al., 2000; Guo et al., 2001; Rocca et al., 2000). RD is frequently increased in patients with MS, reflecting increased diffusion perpendicular to the axon and suggesting a loss of myelination (Fink et al., 2010). Similarly, increases in AD are observed in MS, which is believed to reflect atrophy of white matter fibres contributing to an increase in extracellular water content and greater diffusion along the axon (Sbardella et al., 2013b). Evidence of Wallerian degeneration has been noted in DTI studies of MS. That is, an FA gradient has been identified in patients, such that lower FA has been observed in proximity to lesions, and higher FA values in NAWM distal to lesions (Guo et al., 2001). Authors suggest that this gradient provides further evidence of MS disease processes beyond lesioned tissue.

In pediatric-onset MS, reductions in whole brain FA are consistently noted, relative to healthy controls (Akbar, Giorgio, et al., 2016; Blaschek et al., 2013; Vishwas et al., 2010). The most notable reductions in white matter integrity have been observed in the corpus callosum (i.e., the thick white matter bundle responsible for information-transfer between cerebral hemispheres)(Akbar, Giorgio, et al., 2016; Blaschek et al., 2013; Tillema et al., 2012; Vishwas et al., 2010). Associations between altered diffusion parameters and clinical variables have been noted in pediatric-onset MS patients. For instance longer disease duration has been associated with lower FA (Blaschek et al., 2013). Moreover, higher T2 lesion volume and lower thalamic volume have been related to lower FA and higher AD/RD values (Akbar, Giorgio, et al., 2016).

Diffusion tensor imaging of the cerebellum

In healthy subjects, an approximate grey:white matter ratio of 3:1 has been noted in the cerebellum (Keser et al., 2015). Indeed, much of the cerebellum is made up of foliae that are challenging to quantify via DTI methods, due to alternating tissue types that present with unique diffusion properties (Deppe et al., 2016). As such, the major cerebellar white matter tracts (i.e., the peduncles) are most commonly investigated in DTI studies.

The cerebellar peduncles are responsible for all input to and output from the cerebellum (Kelly & Strick, 2003). Afferent fibres enter the cerebellum through the middle cerebellar peduncle (MCP), carrying information from the cerebral cortex. The inferior cerebellar peduncle (ICP) contains afferent and efferent fibres from the spine and brainstem. Finally, the cerebellum sends information back to the cerebral cortex via the superior cerebellar peduncle (SCP).

Cerebellar microstructural abnormalities in MS

While most studies in MS have reported altered diffusion parameters in NAWM or supratentorial white matter, a small body of literature has examined *cerebellar* white matter abnormalities in this patient population. In general, lower FA and higher RD, and to a lesser extent, higher MD and AD, in the cerebellar peduncles has been noted in MS patients relative to age- and sex-matched healthy controls (Anderson et al., 2011; Deppe et al., 2016; Hannoun et al., 2018; Nicoletti et al., 2017; Preziosa et al., 2014). Such reductions in microstructural integrity have been observed even in patients without cerebellar lesions (Deppe et al., 2016; Hannoun et al., 2018). Notably, the presence of cerebellar lesions appear to impact peduncle microstructural integrity amongst MS patients, with some studies observing lower superior cerebellar peduncle (SCP) FA in relapsing-remitting patients with cerebellar lesions compared to patients without (Nicoletti et al., 2017). Lesions in the cerebellar peduncles are common, with

reports of up to 65% of patients presenting with middle cerebellar peduncle (MCP) lesions and 43% with SCP lesions present documented in prior work (Preziosa et al., 2014).

Different MS subtypes present with varying degrees of diffusion abnormalities of cerebellar white matter, such that patients with secondary progressive MS demonstrate lower FA and higher RD in the MCP compared to patients with relapsing-remitting MS and healthy controls (Anderson et al., 2011). Clinical disability is also related to diffusivity abnormalities of the peduncles. Indeed, one study noted that patients with a high EDSS score (i.e., ≥ 4; "significant disability but able to walk without aid or rest for 500m") demonstrated lower FA and higher MD and RD in the MCP and SCP relative to patients with a low EDSS score (i.e., < 4) (Preziosa et al., 2014). This study, and others, have noted that patients with high levels of clinical disability have higher T2 lesion load and more pronounced cerebellar atrophy (Edwards et al., 1999; Preziosa et al., 2014). Moreover, some studies have noted that higher clinical disability and longer disease duration correlate with lower white matter integrity (i.e., lower FA) (Deppe et al., 2016).

There is a paucity of literature that has examined cerebellar microstructural integrity in pediatric-onset MS. Investigating infratentorial structures such as the cerebellum is an important endeavour, considering that pediatric-onset MS patients present with a higher proportion of infratentorial lesions when compared to adult-onset MS patients matched for disease duration (Waubant et al., 2009b). Indeed, studying infratentorial microstructural integrity may provide further insight into MS disease pathology in pediatric-onset patients. Of the limited research that exists, one study has investigated cerebellar volume reductions in pediatric-onset MS and noted failure of age-expected cerebellar growth relative to healthy controls, most notably in the posterior lobes (Weier et al., 2015). Cerebellar volume reductions were similar in magnitude to

cerebral volume reductions; however, they did not correlate with total brain T2 lesion volume at onset or clinical disability.

Study Two

To our knowledge, there is no existing literature that has examined microstructural integrity of cerebellar subregions in pediatric-onset MS. Investigating cerebellar diffusion abnormalities in more detail in this patient population will help to further characterize disease process. The purpose of Study Two was to examine differences in cerebellar microstructure between pediatric-onset MS patients and healthy controls. Cerebellar volumes were also examined, to compare with the existing literature in pediatric-onset MS. An exploratory analysis comparing patients with and without infratentorial lesions was also conducted to evaluate the impact of proximal disease activity on cerebellar microstructural integrity.

Methods

Participants

Of the 176 participants in Study One, research MRI scans were performed for 152 (86.4%) subjects.

MRI Protocol

Structural MRI was performed on a 3T scanner (varying models at different sites). Each participant completed a standard neuroimaging research protocol outlined in the MRI Standard Operating Procedures from the Montreal Neurological Institute. The following sequences were acquired at each site: T1-weighted MPRAGE (TR 1810ms, TE 3.51ms, TI 1100ms, flip angle 9, 160 slices, voxel size 0.9 x 0.9 x 1 mm^3); 3D FLASH with and without a magnetization transfer pulse to compute magnetization transfer ratio (MTR; TR 33ms, TE 3.86ms, flip angle 10, 192 slices, voxel size 1 x 1 x 1 mm^3, GRAPPA factor 2; dual-angle B1 mapping pair (EPI-SE, TR 4000 ms, TE 18 ms, voxel size 2 x 2 x 5 mm^3, flip angles 60˚ and 120˚); 2D TSE proton density

(PD)-weighted (TR 2200 ms, TE 10 ms, 60 slices, ETL 4, voxel size 1 x 1 x 3 mm^3); 2D 26 TSE T2-weighted (TR 4500 ms, TE 84 ms, 60 slices, ETL 11, voxel size 1 x 1 x 3 mm^3); 3D FLAIR (TR 5000 ms, TE 388 ms, TI 1800 ms, ETL 155, 208 slices, voxel size 1 x 1 x 1 mm^3), DTI (TR 10300 ms, TE 94 ms, 30 diffusion-encoding directions, 50 slices, voxel size 2 x 2 x 2 mm^3, GRAPPA factor 2); T1-weighted pre/post gadolinium (3D FLASH TR 30 ms, TE 6.15 ms, flip angle 27˚, 60 slices, voxel size 1 x 1 x 3 mm^3).

MRI Post-Processing

Lesion Segmentation

Whole brain lesion segmentations were performed at the Montreal Neurological Institute (MNI; Montreal, QC) by trained staff blinded to clinical and behavioural data. For volumetric analyses, the lesions were in-painted on the MPRAGE images to look like the surrounding normally appearing voxels with the Lesion Segmentation Toolbox (Schmidt et al., 2019). Supratentorial and infratentorial lesion volumes were computed using custom MATLAB routines. Lesion maps were manually inspected for the presence/absence of infratentorial lesions using ITK-SNAP (Yushkevich et al., 2006). For 4 patients, only a single voxel was noted in the infratentorium and as such was coded as “no lesion.”

Brain, Thalamus and Cerebellum Segmentation

Normalized whole-brain volume was estimated using SIENAx (Smith, 2002; Smith et al., 2001, 2002). First, the brain and skull were extracted from the T1 image. Then, the brain image was affine-registered to MNI152 space, using the skull image to determine registration scaling (Jenkinson et al., 2002; Jenkinson & Smith, 2001). Notably, the quality of the registration to the MNI152 template was manually inspected for each participant (EDS). Subsequently, tissue-type segmentation with partial volume estimation was carried out (Zhang et al., 2001) in order to

calculate the volumes. Automatic segmentation of the thalamus was obtained on the T1-weighted images using published methods (Datta et al., 2021).

Each 3D T1-weighted dataset underwent automatic cerebellar segmentation via the RASCAL pipeline (Weier, Fonov, Lavoie, Doyon, & Collins, 2014). This method has been previously used to segment the cerebellar lobules of pediatric-onset MS patients (Weier et al., 2015) and has shown that white matter lesions in the cerebellum do not affect the segmentation process. Each subject's T1 image was registered to the 2009 MNI template using the Advanced Normalization Toolkit (ANTs) (Avants et al., 2008). The cerebellar lobes atlas in MNI template space was warped to subject's native space using inverse transformation in ANTs.

For each subject, the different cerebellar lobules were obtained via a multi-atlas segmentation procedure using a majority voting algorithm in ANTs (Avants et al., 2008). Multi-atlas segmentation has been shown to produce more accurate segmentation than single atlas segmentation, reaching the level of inter-rater reliability (i.e., overlap between the automatic method and manual raters is similar to the average inter-rater overlap) (Wang & Yushkevich, 2013; Yushkevich et al., 2010).

To minimize segmentation errors that may happen due to an automatic segmentation procedure, the cerebellar segmentations for all subjects underwent quality control by trained personnel at York University. All segmentation errors were corrected manually in ITK-SNAP (Yushkevich et al., 2006). The following volumes were then extracted using ITK-SNAP: total cerebellar volume, cerebellar anterior lobule volumes (lobules I-V), cerebellar posterior lobule volumes (Crus I/II and lobules VI-X), cerebellar vermis volume, cerebellar peduncle volumes (MCP and SCP), and white matter cores of both hemispheres. Total anterior lobe volume was

computed as the sum of lobules I-V, and total posterior lobe volume was computed as the sum of Crus I/II and lobules VI-IX.

As the data reported in this study were collected at multiple imaging sites, inter-scanner variability in the measures was controlled for by ComBat, an algorithm used to estimate scanner-related differences in the data (Fortin et al., 2017). Following this computation, all volumes were corrected for head size by multiplying each volume by a scaling factor derived from SIENAx. The scaling factor provides a numeric estimate of the degree to which a participant's brain was manipulated in order to fit the MNI152 template, and is calculated by dividing the normalized brain volume by the un-normalized brain volume.

White Matter Microstructure

White matter microstructure was measured via diffusion tensor imaging (DTI). Four measures of water diffusion are reported: fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD). DTI data processing was conducted using the FMRIB Software Library (FSL; www.fmrib.ox.ac.uk/fsl/). Analyses were computed with lesions included in the diffusion-weighted images, as we were interested in the impact of pathology on cerebellar microstructure. Preprocessing of the images corrected for MRI eddy currents and head motion using non-linear registration to a reference volume (b=0) using the eddy tool.

Brain masks were generated using the Brain Extraction Tool (BET) in FSL and applied to the diffusion images to remove the skull and constrain the analyses to only the voxels corresponding to the different brain regions. A diffusion tensor model was fit at each voxel on the skull-stripped diffusion images using DTIFIT tool available in FSL. For each subject, FA and MD maps were generated on a voxel-wise level.

As a result of preprocessing, FA, MD, AD, and RD images were created for each subject on a voxel-wise level for all brain regions. DTI images were manually inspected for registration to the T1 image, and subject scans were eliminated where the cerebellum was cut-off. Mean FA/MD/AD/RD values were estimated (FreeSurfer *mri_segstats*) (Fischl, 2012) for each cerebellar lobule and the cerebellar peduncles by applying the RASCAL segmentation masks. Finally, mean whole brain FA/MD/AD/RD were also estimated. Notably, each DTI metric was harmonized by ComBat separately (i.e., volumes, FA, MD, AD, RD), to control for inter-scanner variability.

Statistical Analyses

Differences in demographic and clinical variables were examined with Welch's t-tests and Mann Whitney-U tests, where appropriate. A threshold of $p \leq .05$ was applied to assess statistical significance of group demographic/clinical comparisons. To examine group differences in volumes (normalized whole brain, grey/white matter, thalamus, cerebellum) and DTI metrics (cerebellar and whole brain FA/MD/AD/RD), multiple linear regressions were computed, with age and sex included as covariates. Group x age and group x sex interactions were also investigated. A quadratic effect of age (i.e., age^2) was investigated and included where model fit was observed. Many models did not demonstrate a quadratic effect. This may be attributed to the cross-sectional nature of the current study, as a quadratic effect of age has been observed in longitudinal studies where growth modelling has been employed. The current model adjusting for age and sex is consistent with prior cross-sectional studies that have examined group differences in cerebellar white matter in MS (Moroso et al., 2017; Weier et al., 2016b).

Models testing brain and cerebellar volumes were computed for only participants ages 16 years and older, as the brain normalization procedure uses a young adult template which may

inflate brain volumes for children with smaller head size. In children, a higher brain to intracranial cavity volume ratio results in inflated normalized brain volumes. As normalized brain volume has been demonstrated to peak in later adolescence (Aubert-Broche et al., 2013), a cut-off of 16 years of age was applied for analyzing normalized volumetric data in the current study. Associations between DTI metrics and clinical outcomes were examined with multiple linear regression (controlling for age and sex) in the MS group.

A supplemental analysis was conducted comparing MS patients with and without infratentorial lesions. To compare MS subgroups with healthy controls, all groups were added to one model. Dummy coding was employed on the "group" variable, with healthy controls as the reference group. In this way, the intercept of each model reflected the mean of the reference group, whereas the regression coefficients for each MS group reflected the MS-Control mean differences.

All models were tested for meeting linear regression assumptions, including normality (Shapiro-Wilk's test and histograms/Q-Q plots), homoscedasticity (Studentized Breusch-Pagan test and plot of residuals vs. predicted values), and linearity (plot of residuals vs. fitted values). Outliers were identified by examining Cook's Distance plots and running sensitivity analyses on potential outlying datapoints. Outliers were removed if they had significant influence on the model. As this is the first study to examine cerebellar subregion microstructure in pediatric-onset MS, a threshold of $p \leq .01$ was applied to assess statistical significance of results, to adjust for multiple comparisons and guard against a false positive effect. All statistical analyses were computed in R (R Core Team, 2019).

Results

Missing data and MRI scan exclusion

A flow-chart outlining missing MRI data and scan exclusion is detailed in **Figure 2.** Of the 152 MRI scans obtained, 11 (7.2%) were unable to be analyzed due to poor image acquisition, error in scanning protocol, and incidental findings. The cerebellum was segmented for 59 of the 68 (86.8%) MS participants and 82 of the 108 healthy control participants (75.9%). Following cerebellar segmentation and DTI preprocessing, 21 scans were removed from the analysis due to failed segmentation, incomplete DTI acquisition, DTI protocol errors, and cut-off cerebellum. The final sample in the DTI analytic dataset included 45 MS participants (66.2% of original sample) and 75 healthy controls (69.4% of original sample). One healthy control and three MS participants had their MRI scan completed more than 3 months following their cognitive evaluation. These individuals were examined, and none were identified as outliers in either Study One or Study Two, as such, they were included in all analyses. Participants included in the DTI analytic dataset did not statistically differ from participants excluded from this analysis on demographic and clinical variables (data shown for MS and healthy control participants in **Supplemental Tables 2 and 3**, respectively). Participants in the volumetric dataset (i.e., ≥16 years) included 35 MS patients and 41 healthy controls.

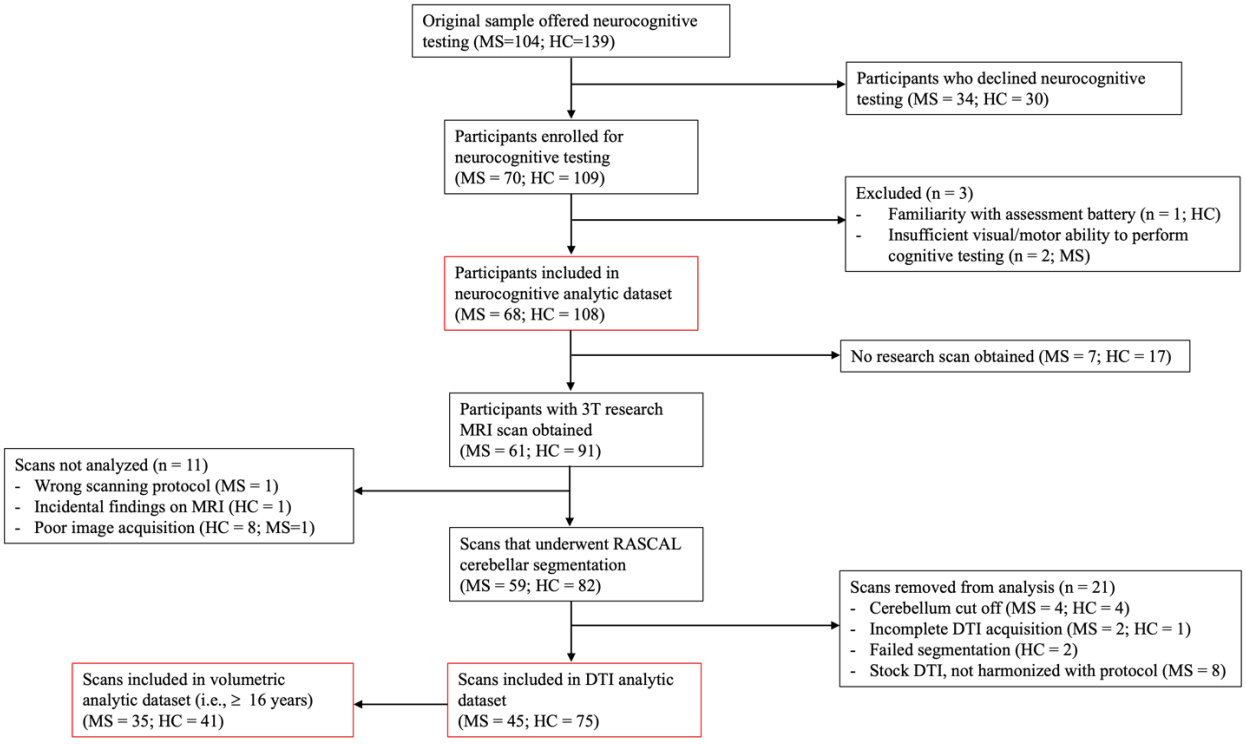

Figure 2. Patient flow-through study and MRI analysis inclusion/exclusion. Boxes in red indicate patients included in analytical dataset.

Group differences in volumetrics

Group differences in MRI volumetrics are presented in **Table 5**. Overall, groups did not statistically differ with respect to normalized cerebellar volumes. Lower normalized brain volume in MS participants compared to healthy controls approached statistical significance (1570.63 ± 70.49 vs. 1596.48 ± 59.97, $p = .04$), as well as lower normalized grey matter volume in the MS group (852.19 ± 57.55 vs. 867.71 ± 40.24, $p = .02$). MS participants demonstrated significantly lower normalized thalamic volumes relative to healthy controls (14.13 ± 1.84 vs. 16.31 ± 1.37, $p < .001$).

Table 5. Differences in normalized cerebellar and brain volumes (cm^3) between MS participants and healthy controls.

	MS (n=35)	HC (n=41)			
Region of Interest (cm3)	**M(SD)**	**M(SD)**	**B(SE)**	***p***	**95% CI**
Total Cerebellum	181.20(19.54)	183.22(12.67)	-1.42(3.88)	.72	-9.15 to 6.31

Anterior Lobes	18.46(2.29)	18.85(1.38)	-0.40(0.44)	.37	-1.28 to 0.48
Posterior Lobes	137.98(15.40)	139.14(11.68)	-0.60(3.22)	.85	-7.03 to 5.83
Cerebellar Peduncles	9.35(1.05)	9.41(0.73)	-0.060(0.22)	.78	-0.49 to 0.37
SCP	0.32(0.043)	0.32(0.045)	-0.004(0.01)	.72	-0.025 to 0.017
MCP	9.04(1.02)	9.09(0.72)	-0.056(0.21)	.79	-0.48 to 0.36
Cerebellar White Matter Core	15.40(2.11)	15.89(1.38)	-0.35(0.42)	.40	-1.20 to 0.49
Normalized Brain Volume	1570.63(70.49)	1596.48(59.97)	-31.94(15.10)	.04	-62.03 to -1.84
Normalized Grey Matter Volume[a]	852.19(57.55)	867.71(40.24)	-20.81(9.06)	.02	-38.74 to -2.87
Normalized White Matter Volume	716.02(44.46)	729.93(29.40)	-12.79(8.97)	.16	-30.69 to 5.10
Normalized Thalamic Volume	14.13(1.84)	16.31(1.37)	-2.28(0.38)	**<.001**	-3.04 to -1.52

Note. All volumes are normalized for head size using the scaling factor derived by SIENAx. Volumes are reported in cm^3.
Models adjusted for age and sex; superscript[a] indicates models adjusted for I(age^2)
Models computed only for participants ages 16 years and older.
Abbreviations. SCP = superior cerebellar peduncle; MCP = middle cerebellar peduncle
Bold indicates $p \leq .01$

Group differences in diffusion metrics

FA group differences

One healthy control was identified as an outlier and removed from all DTI analyses. With respect to the cerebellar diffusion parameters, lower FA in MS relative to healthy controls approached statistical significance in the posterior lobes (0.154 ± 0.01 vs. 0.158 ± 0.01, $p = .04$). Lower FA in the cerebellar peduncles was noted in the MS group, specifically in the middle cerebellar peduncle (MCP; 0.427 ± 0.03 vs. 0.443 ± 0.03, $p = .008$). Finally, MS participants also demonstrated lower whole brain FA (0.182 ± 0.01 vs. 0.188 ± 0.01, $p < .001$). Group differences in FA are presented in **Table 6**.

Table 6. Differences in cerebellar and whole brain fractional anisotropy (FA) between MS and healthy control participants

	MS (n=45)	**HC (n=74)**			
Region of interest	**M(SD)**	**M(SD)**	**B(SE)**	***p***	**95% CI**
Total Cerebellum	0.196(0.01)	0.202(0.01)	-0.006(0.003)	.02	-0.01 to -0.001
Anterior Lobes	0.133(0.01)	0.134(0.01)	-0.001(0.002)	.54	-0.006 to 0.003
Posterior Lobes	0.154(0.01)	0.158(0.01)	-0.005(0.002)	.04	-0.009 to -0.0001

Cerebellar peduncles	0.455(0.04)	0.474(0.04)	-0.020(0.008)	.016	-0.03 to -0.003
SCP	0.483(0.07)	0.504(0.06)	-0.020(0.01)	.08	-0.05 to 0.003
MCP	0.427(0.03)	0.443(0.03)	-0.020(0.006)	**.008**	-0.03 to -0.004
Cerebellar White Matter Core	0.278(0.02)	0.281(0.02)	-0.005(0.004)	.23	-0.01 to 0.003
Whole Brain[a]	0.182(0.01)	0.188(0.01)	-0.008(0.002)	**<.001**	-0.01 to -0.003

Note. Models adjusted for age and sex. Variables with superscript[a] include I(age^2) in the model
Abbreviations. SCP = superior cerebellar peduncle; MCP = middle cerebellar peduncle
Bold indicates $p \leq .01$

MD group differences

No group differences were noted with respect to cerebellar MD. MS participants demonstrated greater whole brain MD relative to healthy controls that approached statistical significance (1.007 ± 0.07 vs. 0.975 ± 0.06, $p = .012$). Group differences in MD are presented in **Table 7**.

Table 7. Differences in cerebellar and whole brain mean diffusivity (MD; $10^{-3}mm^2$) between MS and healthy control participants.

Region of interest	MS (n=45) M(SD)	HC (n=74) M(SD)	B(SE)	*p*	95% CI
Total Cerebellum	0.861(0.06)	0.854(0.06)	0.007(0.009)	.47	-0.01 to 0.02
Anterior Lobes	0.975(0.09)	0.974(0.08)	-0.0001(0.016)	.99	-0.03 to 0.03
Posterior Lobes	0.823(0.05)	0.809(0.03)	0.012(0.008)	.14	-0.004 to 0.03
Cerebellar peduncles	0.876(0.08)	0.874(0.07)	0.001(0.014)	.92	-0.03 to 0.03
SCP	1.045(0.14)	1.055(0.12)	-0.010(0.024)	.69	-0.06 to 0.04
MCP	0.706(0.03)	0.694(0.03)	0.013(0.007)	.06	-0.0003 to 0.03
Cerebellar White Matter Core[a]	0.686(0.03)	0.684(0.03)	0.006(0.005)	.27	-0.005 to 0.02
Whole Brain	1.007(0.07)	0.975(0.06)	0.029(0.01)	.012	0.006 to 0.05

Note. Models adjusted for age and sex. Variables with superscript[a] include I(age^2) in the model
Abbreviations. SCP = superior cerebellar peduncle; MCP = middle cerebellar peduncle
Bold indicates $p \leq .01$

AD group differences

No group differences were noted with respect to cerebellar AD. Greater whole brain AD in MS participants compared to healthy controls approached statistical significance (1.163 ± 0.07 vs. 1.130 ± 0.07, $p = .02$). Group differences in AD are presented in **Table 8**.

Table 8. Differences in cerebellar and whole brain axial diffusivity (AD; $10^{-3}mm^2$) between MS and healthy control participants

Region of interest	MS (n=45) M(SD)	HC (n=74) M(SD)	B(SE)	*p*	95% CI
Total Cerebellum	1.039(0.05)	1.037(0.05)	0.001(0.009)	.88	-0.02 to 0.02
Anterior Lobes	1.100(0.09)	1.099(0.08)	-0.0007(0.017)	.97	-0.03 to 0.03
Posterior Lobes	0.949(0.05)	0.938(0.04)	0.010(0.008)	.24	-0.006 to 0.03
Cerebellar peduncles	1.357(0.09)	1.385(0.10)	-0.027(0.018)	.14	-0.06 to 0.009
SCP	1.650(0.16)	1.708(0.16)	-0.058(0.030)	.06	-0.12 to 0.002
MCP[a]	1.064(0.04)	1.061(0.05)	0.009(0.009)	.31	-0.009 to 0.03
Cerebellar White Matter Core[a]	0.886(0.03)	0.887(0.03)	0.004(0.006)	.54	-0.008 to 0.02
Whole Brain	1.163(0.07)	1.134(0.06)	0.026(0.011)	.02	0.003 to 0.05

Note. Models adjusted for age and sex. Variables with superscript[a] include I(age^2) in the model.
Abbreviations. SCP = superior cerebellar peduncle; MCP = middle cerebellar peduncle
Bold indicates $p \leq .01$

RD group differences

MS participants demonstrated higher RD compared to healthy controls in the MCP (0.528 ± 0.04 vs. 0.509 ± 0.03, $p = .008$). Whole brain RD was also greater in the MS group (0.929 ± 0.07 vs. 0.896 ± 0.06, $p = .009$). Group differences in RD are presented in **Table 9**.

Table 9. Differences in cerebellar and whole brain radial diffusivity (RD; $10^{-3}mm^2$) between MS and healthy control participants

Region of interest	MS (n=45) M(SD)	HC (n=74) M(SD)	B(SE)	*p*	95% CI
Total Cerebellum	0.772(0.06)	0.762(0.04)	0.009(0.009)	.30	-0.008 to 0.03
Anterior Lobes	0.912(0.09)	0.911(0.08)	0.0005(0.016)	.97	-0.03 to 0.03
Posterior Lobes	0.760(0.05)	0.746(0.03)	0.012(0.008)	.11	-0.003 to 0.003
Cerebellar peduncles	0.634(0.08)	0.618(0.06)	0.016(0.014)	.23	-0.01 to 0.04
SCP	0.741(0.15)	0.727(0.12)	0.015(0.025)	.55	-0.03 to 0.06
MCP	0.528(0.04)	0.509(0.03)	0.018(0.007)	**.008**	0.005 to 0.03
Cerebellar White Matter Core	0.586(0.03)	0.582(0.03)	0.005(0.005)	.41	-0.006 to 0.06
Whole Brain	0.929(0.07)	0.896(0.06)	0.030(0.011)	**.009**	0.008 to 0.05

Note. Models adjusted for age and sex.
Abbreviations. SCP = superior cerebellar peduncle; MCP = middle cerebellar peduncle
Bold indicates $p \leq .01$

Interactions with age and sex

No main effect of age or sex was noted on any cerebellar region of interest (i.e., volume or DTI). In addition, no group x age interactions were observed.

Clinical and MRI correlates of cerebellar DTI metrics in the MS group

Clinical and MRI associations were only investigated in MS participants for cerebellar and whole brain DTI parameters that differed between groups. **Supplemental Figures 2 and 3** illustrate the Pearson and Spearman correlation matrices, respectively. All associations were examined with linear regression, controlling for age and sex. No clinical associations with cerebellar FA, MD, AD, or RD were noted at a threshold of $p \leq .01$. Cerebellar DTI associations significant at $p < .05$ are detailed in **Table 10.**

Table 10. Clinical associations with cerebellar DTI metrics in the MS group.

Clinical variable	MRI metric	B(SE)	*p*	95% CI
Age of onset (yr)	Peduncle FA	0.006(0.003)	.04	0.0003 to 0.01
	MCP FA	0.005(0.002)	.04	0.0002 to 0.009
Disease duration (yr)	Peduncle FA	-0.0005(0.0003)	.05	-0.01 to -0.00005
Number of attacks	Posterior Cerebellum FA	-0.004(0.002)	.03	-0.007 to -0.0004
	Peduncle FA	-0.01(0.005)	.03	-0.02 to -0.001
T1 lesion volume	*n.s.*			
T2 lesion volume	*n.s.*			
EDSS	*n.s.*			
Emotional distress	*n.s.*			

Note: Model adjusted for age and sex. Models computed only on DTI metrics that differed between MS and healthy control participants. Values in bold are significant at $p \leq .01$; *n.s.* = non-significant associations at $p < .05$

MS sub-group analysis

MS patients with (n = 26) and without (n = 19) infratentorial lesions at the time of cognitive testing were compared (clinical and demographic data presented in **Table 11)**. Lesion masks were available for 56/68 (82.3%) of patients in the original study sample. Patient groups did not statistically differ with respect to demographic variables. MS patients with infratentorial lesions demonstrated significantly poorer clinical outcomes, including higher EDSS score (p =

.01), higher number of clinical attacks (p = .003), and higher whole-brain T2 lesion volume (p = .001). Groups did not statistically differ with respect to age at disease onset, disease duration, or whole-brain T1 lesion volume.

Table 11. Demographic and clinical characteristics of MS participants with and without infratentorial lesions at time of cognitive testing.

Clinical/Demographic Variable	n	No IT lesion	n	IT lesion(s)	p^a	Cohen's *d*
Age at testing (years; mean, range)	19	17.79(8-27)	26	17.42(13-24)	.75	0.01
Sex (female:male, %female)	19	13:6(68.4)	26	22:4(84.6)	.35[b]	-
Participant education (years, M(SD))	18	11.22(3.57)	26	11.19(2.37)	.97	0.01
Parental education (years, M(SD))	18	13.64(2.19)	25	14.46(1.78)	.11[c]	0.42
Socioeconomic status M(SD)	13	31.35(14.68)	14	37.29(16.80)	.34	0.38
Emotional Distress (#normal:high, %high)	15	8:7(46.7)	19	13:6(31.6)	.59[b]	-
Participant Fatigue (median; range)						
Parent-rated	18	69.44(1.39-100)	25	63.89(42.65-100)	.82	0.07
Participant-rated	18	60.42(38.89-93.06)	26	63.23(26.39-98.61)	.98	0.006
Age at disease onset (years; median,range)	19	15.72(6.28-17.62)	26	14.98(8.65-17.73)	.15[c]	0.31
Disease Duration (years; median,range)	19	0.58(0.33-10.54)	26	2.74(0.42-11.16)	.24[c]	0.06
EDSS (median, range)	19	1(0-2)	26	1.5(0-3)	**.01**[c]	0.74
Number of attacks (median; range)	19	1(0-6)	26	2(1-7)	**.006**[c]	0.69
T2 lesion volume (cm^3; median, range)	19	2.23(0.03-19.95)	26	8.11(0.49-42.76)	**.002**[c]	0.91
T1 lesion volume (cm^3; median, range)	14	0.36(0-3.1)	20	0.72(0-8.96)	.19[c]	0.55

Note. All p values reflect Welch's t-tests, unless otherwise specified; IT = infratentorial; EDSS = Expanded Disability Status Scale; Socioeconomic status measured by the Barratt Simplified Measure of Social Status
[a]Values in bold are significant at $p \leq .05$; [b]Chi-square test; [c]Mann Whitney-U test;

MS group differences in cerebellar MRI and DTI metrics

MS patients with infratentorial lesions present (IT) and absent (nIT) were compared on cerebellar MRI and DTI metrics. Patient groups did not statistically differ with respect to normalized cerebellar or brain volumes (data presented in **Supplemental Table 4**). When DTI

metrics were examined, MCP, cerebellar white matter core, and whole brain microstructure appeared to be reduced in MS patients with infratentorial lesions. That is, they demonstrated higher MCP MD (IT: 0.721 ± 0.03 vs. nIT: 0.686 ± 0.04, p = .002) and AD (IT: 1.079 ± 0.04 vs. nIT: 1.043 ± 0.04, p = .003), relative to patients without infratentorial lesions. Lower FA (IT: 0.420 ± 0.03 vs. nIT: 0.436 ± 0.03; p = .015) and higher RD (IT: 0.541 ± 0.04 vs. nIT: 0.510 ± 0.04; p = .016) in patients with infratentorial lesions approached statistical significance. Higher cerebellar white matter core MD and RD were noted in the MS group with infratentorial lesions (MD: IT: 0.697 ± 0.03 vs. nIT: 0.671 ± 0.03, p = .004; RD: IT: 0.596 ± 0.03 vs. nIT: 0.510 ± 0.04, p = .004), with higher AD approaching statistical significance (IT: 0.897 ± 0.03 vs. nIT: 0..871 ± 0.03 , p = .012). Finally, whole brain FA was significantly lower in the patient group with infratentorial lesions (IT: 0.179 ± 0.01 vs. nIT: 0.187 ± 0.01, p = .005). All comparisons for DTI data between patient groups are presented in **Table 12.**

Table 12. Differences in cerebellar and whole brain DTI metrics between MS patients with infratentorial lesions and MS patients without infratentorial lesions. Data are means (*SD*), unless otherwise specified.

	nIT (n=19)	IT (n=26)	Group difference		
DTI metric	**M(SD)**	**M(SD)**	**B(SE)**	***p***	**95% CI**
mean FA [0 - 1]					
Total Cerebellum FA	0.200(0.02)	0.194(0.01)	0.006(0.005)	.17	-0.003 to 0.02
Anterior Lobe FA	0.137(0.01)	0.130(0.01)	0.006(0.004)	.13	-0.002 to 0.01
Posterior Lobe FA	0.158(0.02)	0.150(0.01)	0.007(0.004)	.10	-0.001 to 0.02
Cerebellar peduncle FA	0.458(0.04)	0.452(0.04)	0.003(0.01)	.82	-0.02 to 0.03
SCP FA	0.480(0.07)	0.486(0.07)	-0.009(0.02)	.67	-0.05 to 0.03
MCP FA	0.436(0.03)	0.420(0.03)	0.02(0.009)	.015	0.005 to 0.04
White Matter Core FA	0.281(0.02)	0.272(0.02)	0.006(0.006)	.26	-0.006 to 0.02
Whole Brain FA[a]	0.187(0.01)	0.179(0.01)	0.01(0.004)	**.005**	0.003 to 0.018
mean MD (10^-3 mm^2)					
Total Cerebellar MD	0.840(0.05)	0.877(0.06)	-0.03(0.02)	.11	-0.06 to 0.006
Anterior Lobe MD	0.948(0.10)	0.995(0.08)	-0.04(0.07)	.15	-0.10 to 0.02
Posterior Lobe MD	0.803(0.04)	0.837(0.05)	-0.03(0.01)	.04	-0.06 to -0.0009

Cerebellar peduncle MD	0.858(0.08)	0.889(0.07)	-0.03(0.02)	.17	-0.08 to 0.01
SCP MD	1.029(0.17)	1.056(0.12)	-0.03(0.04)	.48	-0.12 to 0.06
MCP MD	0.686(0.04)	0.721(0.03)	-0.04(0.01)	**.002**	-0.06 to -0.01
White Matter Core MD	0.671(0.03)	0.697(0.03)	-0.03(0.009)	**.004**	-0.04 to -0.009
Whole Brain MD	0.983(0.06)	1.024(0.07)	-0.04(0.02)	.052	-0.08 to 0.0003
mean RD (10^-3 mm^2)					
Total Cerebellar RD	0.751(0.05)	0.788(0.06)	-0.03(0.02)	.06	-0.07 to 0.0008
Anterior Lobe RD	0.885(0.10)	0.932(0.08)	-0.04(0.03)	.15	-0.10 to 0.02
Posterior Lobe RD	0.740(0.04)	0.775(0.05)	-0.03(0.02)	.04	-0.06 to -0.002
Cerebellar peduncle RD	0.620(0.09)	0.645(0.08)	-0.03(0.03)	.32	-0.08 to 0.03
SCP RD	0.730(0.17)	0.749(0.13)	-0.02(0.05)	.67	-0.12 to 0.07
MCP RD	0.510(0.04)	0.541(0.04)	-0.03(0.01)	.016	-0.06 to -0.006
White Matter Core RD	0.573(0.03)	0.596(0.03)	-0.03(0.009)	**.004**	-0.05 to -0.01
Whole Brain RD	0.906(0.06)	0.946(0.07)	-0.04(0.02)	.06	-0.08 to 0.001
mean AD (10^-3 mm^2)					
Total Cerebellar AD	1.018(0.04)	1.050(0.05)	-0.03(0.02)	.10	-0.06 to 0.005
Anterior Lobe AD	1.072(0.10)	1.120(0.09)	-0.04(0.03)	.14	-0.1 to 0.01
Posterior Lobe AD	0.931(0.04)	0.962(0.05)	-0.03(0.02)	.07	-0.06 to 0.002
Cerebellar peduncle AD	1.33(0.09)	1.37(0.08)	-0.05(0.03)	.07	-1.0 to 0.005
SCP AD	0.730(0.17)	0.749(0.13)	-0.02(0.05)	.67	-0.1 to 0.07
MCP AD	1.043(0.04)	1.079(0.04)	-0.04(0.01)	**.003**	-0.06 to -0.01
White Matter Core AD	0.871(0.03)	0.897(0.03)	-0.02(0.008)	.012	-0.04 to -0.005
Whole Brain AD	1.139(0.06)	1.181(0.07)	-0.42(0.02)	.05	-0.083 to -0.0007

Note. Models adjusted for age and sex; superscript[a] indicates models adjusted for I(age^2) Bold indicates $p \leq .01$; IT = infratentorial lesions present; nIT = infratentorial lesions absent

An additional analysis was conducted to compare each MS subgroup to healthy controls, within the major cerebellar subregions. **Table 13** summarizes the DTI findings comparing patient subgroups (i.e., nIT vs. IT) to healthy controls. Results indicate that MS patients without infratentorial lesions did not statistically differ from healthy controls with respect to cerebellar white matter. In contrast, patients who presented with infratentorial lesions had significantly reduced white matter integrity of the cerebellar posterior lobe, MCP, and whole brain, compared to healthy controls. Notably, MS subgroups did not statistically differ from controls with respect to cerebellar or whole brain volumes, with the exception of thalamic volume, which was reduced

in both MS subgroups (Intercept = 17.84; IT: B(SE) = -2.57(0.46), $p < .001$, 95% CI = -3.48 to -1.66; nIT: B(SE) = -1.90(0.50), $p < .001$, 95% CI = -2.89 to -0.91).

Table 13. Differences in cerebellar and whole brain DTI metrics (FA/MD/RD/AD) in MS patient subgroups with infratentorial lesions (IT) and without infratentorial lesions(nIT), compared to healthy controls (HC). Data are means (*SD*), unless otherwise specified.

					IT			nIT		
DTI metric	**nIT (n=19)**	**IT (n=26)**	**HC (n=74)**	**Int.**	**B(SE)**	***p***	**95% CI**	**B(SE)**	***p***	**95% CI**
FA [0 – 1]										
Total Cerebellum	0.200(0.02)	0.194(0.01)	0.203(0.01)	0.199	-0.008(0.003)	**.003**	-0.01 to -0.003	-0.002(0.003)	.56	-0.01 to 0.01
Anterior Lobes[a]	0.137(0.01)	0.130(0.01)	0.135(0.01)	0.105	-0.006(0.003)	.04	-0.01 to -0.0003	-0.002(0.003)	.59	-0.004 to 0.007
Posterior Lobes	0.158(0.02)	0.150(0.01)	0.160(0.01)	0.161	-0.008(0.003)	**.005**	-0.01 to -0.002	-0.0005(0.003)	.88	-0.01 to -0.002
Peduncles	0.458(0.04)	0.452(0.04)	0.474(0.04)	0.452	-0.020(0.009)	.03	-0.04 to -0.002	-0.016(0.010)	.12	-0.04 to 0.004
SCP	0.480(0.07)	0.486(0.07)	0.504(0.06)	0.472	-0.019(0.015)	.22	-0.05 to 0.01	-0.025(0.017)	.13	-0.06 to 0.008
MCP	0.443(0.03)	0.420(0.03)	0.444(0.03)	0.432	-0.022(0.007)	**.002**	-0.04 to -0.008	-0.007(0.008)	.38	-0.02 to 0.008
WMC	0.281(0.02)	0.272(0.02)	0.283(0.02)	0.278	-0.008(0.005)	.10	-0.02 to 0.002	0.0005(0.005)	.93	-0.01 to 0.01
Whole Brain[a]	0.188(0.01)	0.179(0.01)	0.189(0.01)	0.15	-0.012(0.003)	**<.001**	-0.02 to -0.007	-0.003(0.003)	.32	-0.008 to 0.003
MD ($10^{-3}mm^2$)										
Total Cerebellum	0.840(0.05)	0.872(0.05)	0.849(0.06)	0.853	0.022(0.011)	.04	0.0007 to 0.04	-0.014(0.012)	.25	-0.04 to 0.01
Anterior Lobes	0.948(0.10)	0.995(0.08)	0.969(0.09)	0.984	0.020(0.019)	.32	-0.02 to 0.06	-0.026(0.022)	.23	-0.07 to 0.02
Posterior Lobes	0.803(0.04)	0.837(0.05)	0.805(0.05)	0.793	0.026(0.009)	**.006**	0.008 to 0.05	-0.007(0.010)	.49	-0.03 to 0.01
Peduncles	0.858(0.08)	0.889(0.07)	0.87(0.08)	0.910	0.014(0.016)	.39	-0.02 to 0.05	-0.015(0.018)	.40	-0.05 to 0.02
SCP	1.029(0.17)	1.056(0.12)	1.050(0.13)	1.109	0.0007(0.029)	.98	-0.06 to 0.06	-0.024(0.033)	.47	-0.09 to 0.04
MCP	0.686(0.04)	0.721(0.03)	0.690(0.04)	0.711	0.027(0.008)	**<.001**	0.01 to 0.04	-0.007(0.008)	.40	-0.02 to 0.01
WMC[a]	0.671(0.03)	0.697(0.03)	0.681(0.04)	0.764	0.019(0.006)	**.003**	0.006 to 0.03	-0.010(0.007)	.15	-0.02 to 0.004
Whole Brain	0.983(0.06)	1.024(0.07)	0.970(0.06)	0.907	0.047(0.014)	**<.001**	0.02 to 0.07	0.005(0.015)	.73	-0.03 to 0.04
RD ($10^{-3}mm^2$)										
Total Cerebellum	0.751(0.05)	0.788(0.06)	0.757(0.06)	0.761	0.025(0.011)	.02	0.003 to 0.05	-0.011(0.012)	.37	-0.03 to 0.01

Anterior Lobes	0.885(0.10)	0.932(0.08)	0.906(0.09)	0.986	0.025(0.020)	.22	-0.02 to 0.07	-0.023(0.022)	.28	-0.07 to 0.02
Posterior Lobes	0.740(0.04)	0.775(0.05)	0.741(0.05)	0.727	0.027(0.009)	**.004**	0.009 to 0.05	-0.007(0.010)	.49	-0.03 to 0.01
Peduncles	0.620(0.09)	0.645(0.08)	0.614(0.07)	0.659	0.026(0.016)	.11	-0.006 to 0.06	0.003(0.018)	.86	-0.03 to 0.04
SCP	0.730(0.17)	0.749(0.13)	0.723(0.12)	0.789	0.020(0.030)	.46	-0.04 to 0.08	0.005(0.033)	.87	-0.06 to 0.07
MCP	0.510(0.04)	0.541(0.04)	0.506(0.04)	0.528	0.031(0.008)	**<.001**	0.02 to 0.05	0.001(0.009)	.89	-0.02 to 0.02
WMC[a]	0.570(0.03)	0.596(0.03)	0.579(0.04)	0.653	0.019(0.007)	**.006**	0.006 to 0.03	-0.007(0.007)	.35	-0.02 to 0.007
Whole Brain	0.906(0.06)	0.946(0.07)	0.891(0.07)	0.832	0.048(0.014)	**<.001**	0.02 to 0.08	0.007(0.015)	.65	-0.02 to 0.04
AD ($10^{-3}mm^2$)										
Total Cerebellum	1.018(0.04)	1.050(0.05)	1.032(0.06)	1.038	0.017(0.011)	.13	-0.005 to 0.04	-0.019(0.012)	.13	-0.04 to 0.006
Anterior Lobes	1.072(0.10)	1.120(0.09)	1.094(0.10)	1.110	0.019(0.020)	.34	-0.02 to 0.06	-0.027(0.022)	.23	-0.07 to 0.02
Posterior Lobes	0.931(0.04)	0.962(0.05)	0.933(0.05)	0.923	0.023(0.010)	.019	0.004 to 0.04	-0.008(0.011)	.46	-0.03 to 0.01
Peduncles	1.33(0.09)	1.37(0.08)	1.378(0.11)	1.421	-0.009(0.022)	.66	-0.05 to 0.03	-0.050(0.024)	.041	-0.10 to -0.002
SCP	0.730(0.17)	0.749(0.13)	1.700(0.17)	1.759	-0.039(0.037)	.29	-0.11 to 0.03	-0.082(0.041)	.046	-0.16 to -0.001
MCP[a]	1.043(0.04)	1.079(0.04)	1.056(0.07)	1.196	0.028(0.011)	.011	0.006 to 0.05	-0.013(0.012)	.27	-0.04 to 0.010
WMC[a]	0.875(0.03)	0.897(0.03)	0.884(0.04)	0.982	0.017(0.007)	.016	0.003 to 0.03	-0.013(0.008)	.10	-0.03 to 0.002
Whole Brain	1.139(0.06)	1.181(0.07)	1.130(0.07)	1.068	0.044(0.013)	**.001**	0.02 to 0.07	0.0016(0.015)	.92	-0.03 to 0.03

Note. Models adjusted for age and sex; superscript[a] indicates models adjusted for I(age^2); Bold indicates $p \leq .01$; IT = infratentorial lesions present; nIT= no infratentorial lesions; SCP = superior cerebellar peduncle; MCP = middle cerebellar peduncle; WMC = white matter core

Discussion

In Study Two, differences in cerebellar microstructure and volume were examined in pediatric-onset MS patients compared to healthy controls. Notably, DTI parameters of the cerebellum distinguished groups, whereas cerebellar volumes did not. Overall, group differences in white matter integrity appeared to be driven by the MS group with infratentorial lesions, as patients without infratentorial lesions did not statistically differ from controls on any cerebellar or whole brain DTI parameters. As expected, the presence of infratentorial lesions reduces white matter integrity of infratentorial structures like the cerebellum. The patient group with infratentorial lesions showed reduced microstructural integrity of cerebellar white matter, specifically the MCP and white matter core, as well as a trend for lower posterior lobe integrity. Reductions in whole brain white matter integrity were also observed.

The mean disease duration for the cohort of MS patients analyzed in this study is approximately 3 years. This may explain why MS patients did not display a statistically significant reduction in cerebellar volumes, relative to age and sex-matched healthy controls. This finding is consistent with Weier et al. (2016) who did not observe cerebellar volume reductions in a sample of 28 pediatric-onset MS patients with a mean disease duration of 4.6 years. Patients in these study cohorts may have been too early in the disease progression to present with significant cerebellar volume reduction. Nevertheless, our data are inconsistent with prior research that has noted failure of age-expected cerebellar volume in pediatric-onset MS patients followed approximately 1-2 years after disease onset, and for an additional 3.5 years (De Meo et al., 2019).

Interestingly, normalized brain volume differences between MS patients and healthy controls did not meet our threshold for statistical significance when patients were stratified by

the presence/absence of infratentorial lesions. This is likely due to decreased power in the MS subgroups, as the combined MS patient sample demonstrated reduced normalized brain volumes relative to healthy controls that approached statistical significance. Past research from our group has noted a failure of age-expected growth in brain volumes of pediatric-onset MS patients (Aubert-Broche et al., 2014); however, such studies had access to multiple MRI scans (2-11) per MS participant. In the current study, we did not have longitudinal data to assess brain growth trajectories and detect group differences. Normalized thalamic volume demonstrated the most robust volumetric reductions in both MS patient subgroups, relative to healthy controls, but did not differ statistically between patient groups. This is consistent with past research in pediatric-onset MS that has noted the thalamus as particularly sensitive to MS pathology, showing pronounced deviations from age-expected growth (Fadda et al., 2019; Kerbrat et al., 2012; Till, Ghassemi, et al., 2011). Notably, normalized thalamic volume was the only MRI metric observed to be significantly reduced in MS patients without infratentorial lesions, relative to healthy controls. As such, the potential for the development of cognitive dysfunction is present in this patient group, given the well-documented relationship between thalamic volume and cognitive impairment in pediatric-onset MS (Till, Ghassemi, et al., 2011). Recent neuroimaging studies have highlighted that neurodegeneration in MS begins in network "hub" areas such as the thalamus, among others (Eshaghi et al., 2018). Indeed, structural damage is rarely confined to a single brain region, but damage to hub regions likely contributes more greatly to changes in the flow of information through both short and long-range brain networks (Fornito et al., 2015). Our study demonstrates that thalamic volume is more sensitive than cerebellar volumes in distinguishing pediatric-onset MS patients from healthy controls.

To our knowledge, this is the first study to examine cerebellar subregion microstructure in pediatric-onset MS patients. In general, the cerebellar peduncles were the most sensitive cerebellar subregion in detecting reduced microstructural integrity in the MS group. Reduced cerebellar microstructure was most apparent among patients with infratentorial lesions. Specifically, the MCP showed reduced FA and higher MD and RD in patients with infratentorial lesions, relative to controls and patients without infratentorial lesions. These findings may be interpreted as demyelination taking place in the MCP, as RD has been related to myelin content in post-mortem studies of MS (Moll et al., 2011). Moreover, increased clinical disability (EDSS score) has been related to lower FA and higher MD of the MCP (Preziosa et al., 2014). Similarly, MS patients with infratentorial lesions in the current study were identified as having a more severe disease course, presenting with higher EDSS scores, a greater number of clinical attacks, higher whole brain T2 lesion volume, and lower whole-brain microstructural integrity. These patients demonstrated greater disruption to major white matter tracts in the cerebellum, as evidenced by higher diffusivity metrics noted in the MCP and the white matter core. As such, the presence of infratentorial lesions may reflect a more aggressive disease course. A recent study of pediatric-onset MS patients noted an association between increased infratentorial lesion accumulation and greater whole brain atrophy (Bartels et al., 2019). Moreover, infratentorial lesions have been associated with increased long-term disability in adult-onset MS (Minneboo et al., 2004). In 2020, a consensus paper was released, which included infratentorial lesions as a potential parameter associated with more aggressive disease course in MS (Iacobaeus et al., 2020), highlighting the need for further research in this regard.

Alterations in MCP white matter integrity have been detected in other neurological and psychiatric populations, including schizophrenia (Okugawa et al., 2005), and stroke (Prakash et

al., 2009), as well as in pediatric neurodevelopmental disorders, such as autism spectrum disorder (Shukla et al., 2010; Sivaswamy et al., 2010), and attention-deficit/hyperactivity disorder (Ashtari et al., 2005). This white matter bundle comprises the major tract containing afferent fibres that receive information from the cortex via the pons (Nicoletti et al., 2017). Presumably, disruptions to MCP microstructure negatively affect the cerebellum's access to motor, cognitive and limbic afferent information arriving from the cerebral cortex (Tobyne et al., 2018). As noted previously, the cerebellum has more recently been implicated in cognitive functioning, beyond its historically recognized role in motor coordination (Schmahmann, 2019). As such, in addition to motor disruption, reduced MCP fibre integrity is expected to impact a variety of cognitive functions, including working memory, language, executive skills, and reasoning (Schmahmann, 2019; Schmahmann & Sherman, 1998; Tobyne et al., 2018). Indeed, Tobyne et al. (2018) noted a significant association between MCP lesions and cognitive impairment, suggesting the functional implications of MCP atrophy in MS.

Lower white matter integrity of the cerebellar white matter core (i.e., higher MD and RD) was also observed in patients with infratentorial lesions relative to healthy controls and patients without infratentorial lesions. The white matter core of the cerebellum contains the deep cerebellar nuclei (i.e., the dentate, emboliform, globose, and fastigii nuclei)(Weier, Fonov, et al., 2014). Specifically, the dentate nucleus is the largest and represents the "main output station" of the cerebellum, sending cerebellar efferents to the cortex via the SCP, the red nucleus, and the thalamus (Bond et al., 2017; Kelly & Strick, 2003; Nicoletti et al., 2017). The dentate nucleus is a predilection site for cerebellar pathology in MS, and post-mortem studies have noted synaptic loss of in this area (Albert et al., 2017). Some recent literature has noted reduced white matter integrity (i.e., lower FA) of the right dentate nucleus in RRMS patients, relative to healthy

controls, which correlated with poorer verbal fluency and memory, as well as higher fatigue scores (Nicoletti et al., 2017). Disruption to MCP and SCP white matter integrity also correlated with poorer cognitive performance, which authors postulate may be a result of structural disconnection between the cerebellum and the cortex. The impact of the cerebellar white matter on cognitive outcomes will be further elaborated upon in Study Three.

Finally, lower white matter integrity (i.e., FA) in the cerebellar posterior lobes in MS patients, relative to controls, approached statistical significance. Previous studies have observed that the posterior lobes of the cerebellum are implicated in a range of cognitive processes, including working memory (Chen & Desmond, 2005), spatial processing (Stoodley et al., 2016), language (Stoodley, 2012), emotional processing and social cognition (George et al., 1993; Lane et al., 1997; Lee et al., 2004; Paradiso et al., 1999). In adult MS, tractography methods have been used to demonstrate that greater structural connectivity of the cerebellar posterior lobes is associated with better information processing speed performance (Bozzali et al., 2013). Other studies have observed impaired working memory associated with reduced posterior lobe white matter integrity in adult MS (Moroso, Ruet, Lamargue-Hamel, Munsch, Deloire, Coupé, Charré-Morin, et al., 2017). Information processing speed and working memory are cognitive processes frequently impacted in pediatric-onset MS (Portaccio et al., 2021), which has implications for overall cognitive development (Kail & Salthouse, 1994). Nevertheless, diffusion parameters in the cerebellar lobes should be interpreted with caution, given the alternating grey and white matter tissue types in these subregions (i.e., partial volume effects) and tightly folding fibre bundles (Deppe et al., 2016). As such, diffusivity information within these regions has a high potential for misinterpretation. Given these methodological limitations, findings within more uniform fibre bundles, such as the cerebellar peduncles are regarded as more reliable (Deppe et

al., 2016). Methodological considerations for the interpretation of diffusion parameters within the cerebellum are elaborated upon in subsequent sections.

In contrast with some previous research, sex differences were not observed in the current study. One study that examined global white matter microstructural growth trajectories in pediatric-onset MS has noted that females may show a steeper decline in white matter integrity (i.e., faster rate of MD increase) than males, when controlling for age (Longoni et al., 2017). Limited research has examined sex differences within the cerebellum in the context of pediatric-onset MS. One study demonstrated that cerebellar volume growth curves peaked earlier in girls than in boys, in both healthy control and pediatric-onset MS groups (Weier, Fonov, et al., 2015). The discrepancy in results with the current study may be explained by age at MRI acquisition. That is, the mean age at first scan for healthy control and MS participants in Weier et al. (2015) was 10.77 and 12.75 years, respectively, with a mean follow-up time of approximately 2-3 years. The current study was cross-sectional in nature, and the average age of healthy control and MS participants was 17.04 and 18.25 years, respectively. As such, it is possible that sex differences were not noted in the current study because participants were generally in late adolescence and early adulthood, where such differences are less apparent in caudal regions of the brain (i.e., sex differences in cerebellar white matter may be more apparent in earlier stages of development). Indeed, some developmental studies of healthy youth have noted that cerebellar white matter and peduncles reach complete maturation (i.e., adult levels) in mid-adolescence (Simmonds et al., 2014), with males demonstrating more protracted white matter development than females (Asato et al., 2010). Puberty has been noted as a factor that may contribute to sex differences in white matter development. That is, puberty onset typically occurs in females 2-3 years earlier than in males, and reaching puberty is associated with increases in white matter integrity (i.e., decreases

in RD and increases in FA)(Asato et al., 2010). Research in this field is limited, and as such, the mechanism driving sex differences in white matter development remains to be fully elucidated.

Summary of Study Two findings

To date, most studies in adult and pediatric-onset MS have examined microstructural abnormalities in normal appearing white matter or supratentorial white matter. There is a paucity of research investigating infratentorial white matter in this patient population. This, in part, is due to challenges with respect to image acquisition of the infratentorium and difficulties obtaining reliable DTI parameters in regions of the brain with crossing fibres and varying tissue types, like the cerebellum. In Study Two, we observed that DTI is a sensitive tool for evaluating the integrity of major cerebellar white matter tracts, particularly the MCP, in pediatric-onset MS. In addition, diffusion parameters of the cerebellar peduncles and white matter core appear to distinguish patients with infratentorial lesions from patients without infratentorial lesions. The functional implications of these changes in cerebellar microstructure are further investigated and discussed in Study Three.

Chapter 4: Cerebellar White Matter as a Predictor of Cognitive Efficiency in Pediatric-Onset MS

In the last decade, the cerebellum has received more attention with respect to its involvement in cognition. “The little brain” is no longer regarded as uniquely responsible for motor coordination, and most of the human cerebellum is in fact dedicated to regulating cognitive processes. The impact of the cerebellum on cognition in MS has largely been understudied, particularly in pediatric-onset MS. The following chapter will highlight how this oft-ignored region of the brain contributes to cognitive outcomes in adult-onset MS, and the emerging literature citing its role in pediatric-onset MS.

Functional topography of the human cerebellum

Topographically precise regions of the cerebellum are intimately linked with the cerebral cortex through feedforward (i.e., the corticopontine-pontocerebellar projection) and feedback (i.e., the cerebello-thalamocortical projection) loops (Schmahmann, 2019). The feedforward projections connect the cortex to the cerebellum via the middle cerebellar peduncle (MCP); whereas feedback projections are facilitated via the superior cerebellar peduncle (SCP) (Nicoletti et al., 2017). The cerebellum has been regarded as a dichotomous structure, such that the anterior lobes (lobules I-V, including lobule VIII) represent the “sensorimotor cerebellum” based on its intimate circuitry with the motor/premotor cortex and spinal afferents, whereas the posterior lobes (lobules VI, VII, Crus I/II, IX, X) represent the “cognitive cerebellum,” due to its connections with association areas of the cerebral cortex that are responsible for higher order cognitive processes (Buckner et al., 2011). While many studies have focused on the structural-functional relationships in specific cerebellar lobules, recent research has noted that functional divisions of the cerebellum are not well-explained by lobular boundaries, but that functional regions often span multiple cerebellar lobules (King et al., 2019). It is worth noting that, much

like the cerebrum, *most* of the human cerebellum (i.e., approximately 80%) is occupied by networks dedicated to top-down regulatory processes. A recent study examining resting-state functional connectivity of the cerebellum in 10 healthy subjects noted that the frontoparietal network is disproportionately expanded in the cerebellum, relative to the cerebral cortex (2.3-fold greater relative representation) (Marek et al., 2018). In addition, this study noted prominent temporal lags in cerebellar blood-oxygen level dependent (BOLD) signals, relative to cortical BOLD signals in association networks (i.e., default-mode, frontoparietal and dorsal/ventral attention), compared to motor networks. These findings highlight the role of the cerebellum as the "final destination" for signals propagating through cortico-cerebellar networks, supporting the cerebellum's role in supervised learning and error signaling (Dosenbach et al., 2007; Fiez et al., 1992; Marek et al., 2018). Such "experience-driven learning" as facilitated by cortico-cerebellar functional connectivity may be critical in the development and maturation of inhibitory and performance-monitoring processes (Rubia et al., 2007).

Recent literature has focused on the functional connectivity between the cerebellum and cortical association networks in adult MS patients. Changes in long-range functional connectivity of cortico-cerebellar networks have been observed in MS (Pasqua et al., 2021; Savini et al., 2019), as well as decreased local connectivity within the cerebellum (Dogonowski et al., 2014). Some studies have observed regional functional connectivity of the cerebellum (i.e., connectivity between cerebellar lobules/hemispheres) to be more sensitive than regional cortical functional connectivity in distinguishing MS patients from healthy controls (Dogonowski et al., 2014). Moreover, lower cerebellar functional connectivity has been related to increased physical disability (i.e., EDSS score) and increased peduncle lesion load (Dogonowski et al., 2014). Some studies have noted cerebellar functional connectivity changes (i.e., increases and decreases with

different association areas) only in progressive MS subtypes (Schoonheim et al., 2021). In secondary progressive MS, higher functional connectivity between the cerebellum and the default mode network has been related to working memory and information processing speed (Schoonheim et al., 2021). In addition, higher functional connectivity between the default-mode network and the cerebellum has been associated with greater information processing speed performance in both cognitively impaired and cognitively preserved MS patients (Savini et al., 2019). One study observed that increased functional connectivity between the cerebellum and the right medial temporal cortex as well as the left parieto-occipital cortex associated with better performance on a processing speed task (Pasqua et al., 2021). This study also noted that this relationship was explained by infratentorial lesion load and cerebellar atrophy (Pasqua et al., 2021). How cerebellar pathology influences cognition in MS remains unclear. Investigating the impact of cerebellar pathology on clinical and cognitive outcomes is an important field of study, particularly in pediatric-onset MS patients, who experience higher infratentorial lesion load, relative to adult-onset MS patients matched for disease duration (Waubant et al., 2009).

Cerebellar abnormalities contribute to clinical disability and cognitive dysfunction in MS

Cerebellar pathology is common in MS (Calabrese et al., 2010; Kutzelnigg et al., 2007), with some studies noting cerebellar T2 lesions in approximately 50% of pediatric-onset MS patients (De Meo, Bonacchi, et al., 2021). Post-mortem studies of MS patients have identified widespread demyelination in the cerebellar cortex, with relative axonal and neuronal preservation (Kutzelnigg et al., 2007). Damage to the cerebellum disrupts cortico-cerebellar circuitry. Given the cerebellum's role in coordinating cognitive processes, an increasing body of literature has been dedicated to investigating cognitive dysfunction in the context of MS-related cerebellar pathology (Weier, Banwell, et al., 2015). Specifically, lesions in the bilateral MCP

have been associated with the presence of cognitive impairment in MS (Mesaros et al., 2012; Tobyne et al., 2018; Weier, Penner, et al., 2014), particularly information processing speed deficits (Weier, Penner, et al., 2014). Moreover, increased physical disability has been associated with higher MCP and SCP lesion load (Preziosa et al., 2014). Specifically, lesions of the MCP disrupt cerebellar access to afferents from the cortex carrying motor and cognitive-affective information (Parmar et al., 2018), and subsequently impact cerebellar efferents to the cortex carrying information regarding motor coordination and cognitive regulation. Consequently, impairment in cognitive processing may ensue as a result of cerebellar disconnection from cortical association areas.

Cerebellar white matter functional correlations

A small body of literature has addressed the relationship between cerebellar microstructural abnormalities and cognitive processing in MS. In general, reduced white matter integrity of the cerebellar peduncles and lobules has been observed (Bozzali et al., 2013; Deppe et al., 2016; Mesaros et al., 2012; Moroso, Ruet, Lamargue-Hamel, Munsch, Deloire, Coupé, Charré-Morin, et al., 2017; Preziosa et al., 2014; Schoonheim et al., 2021), including the current study (i.e., Study Two). This is an important area of research, given the widespread demyelination observed in the cerebellum in post-mortem studies of MS (Kutzelnigg et al., 2007). Some studies have investigated the association between cerebellar white matter and cognitive outcomes. Using random forest analysis, Mesaros et al. (2012) observed that cerebellar peduncle (i.e., MCP/SCP) FA and MD were among the top 10 most important MRI variables in classifying MS patients as impaired on a variety of cognitive tasks, including information processing speed, working memory and verbal memory. In addition, Moroso et al. (2017) noted that SCP FA explained 31% of the variance in processing speed and working memory

performance among relapsing-remitting MS patients. This study also examined white matter integrity within the cerebellar lobules and noted a significant contribution of lobule VI FA to these cognitive processes.

While the relationship between cerebellar lobule microstructure and cognition in MS is an understudied area, it is also a methodologically challenging area of research. Cerebellar lobule morphology of tightly folded and crossing fibres renders methods such as DTI subject to significant error (Deppe et al., 2016). As such, research of this nature should be interpreted with caution. In contrast, microstructure with more directionally coherent fibres, such as the cerebellar peduncles, provide more reliable DTI metrics (Deppe et al., 2016).

Study Three

The aforementioned studies have all investigated cerebellar contributions to cognition in adult-onset MS. To date, only one study has examined the role of the cerebellum in cognitive processing in pediatric-onset MS patients. This study observed that cerebellar posterior lobe volume predicted information processing speed and vocabulary performance in MS patients, despite presenting with normal cerebellar volumes relative to healthy controls (Weier et al., 2016). Notably, the cognitive battery that was included in the aforementioned study was limited in breadth. As such, there is a need to further investigate the role of the cerebellum in cognition among pediatric-onset MS patients.

The aim of Study Three was to determine the contribution of cerebellar white matter microstructure to cognitive efficiency in pediatric-onset MS, compared to healthy controls. Cerebellar white matter was investigated, given the evidence of demyelination and white matter disruption of the cerebellum in MS. As such, stronger associations were expected in MS patients compared to healthy controls, particularly in patients with more significant disease pathology

(i.e., greater total T2 lesion volume and infratentorial lesions present). Subregions including the cerebellar peduncles and white matter core were chosen as regions of interest for this analysis, given the stronger reliability of DTI analyses in thick white matter bundles, compared to the cerebellar lobes. In Study Two, the presence of infratentorial lesions was identified as a useful factor in distinguishing MS patients on disease severity. That is, patients with infratentorial lesions had higher T2 lesion volume, lower whole brain and MCP white matter integrity, higher physical disability, and a higher number of clinical attacks. As such, an exploratory analysis comparing MS patients with and without infratentorial lesions was also conducted, to compare how cerebellar white matter integrity contributes to cognitive efficiency in patients with disease pathology in the infratentorium.

Methods

Participants with DTI analyses conducted in Study Two (MS=45; HC=75) were included in Study Three. All cognitive testing methods and neuroimaging protocol and processing are outlined in Study One and Study Two, respectively.

Statistical Analysis

To investigate whether cerebellar microstructure (i.e., FA, MD, AD, RD) predicts cognitive efficiency (i.e., PCNB efficiency z-score), multiple linear regression analyses were conducted for each cerebellar white matter subregion (i.e., SCP, MCP, cerebellar white matter core), as well as for whole brain.

Models were computed for the MS group and healthy controls separately. The model was as follows:

$$PCNB\ efficiency \sim age + I(age^2) + sex + parental\ education + (T2\ lesion\ volume) + cerebellar\ metric$$

where the *cerebellar metric* referred to DTI measures or volume. Each cerebellar subregion was computed in its own model. Parental education data were available for 68 HC and 43 MS participants for the Study Three models. Notably, total T2 lesion volume was only added to the MS group models, to adjust for the impact of atrophy on cognitive performance.

All models were assessed for homogeneity of variance, normality, collinearity, and linearity. Outliers were assessed via Cook's D plots and examining boxplots. Sensitivity analyses were computed when potential outliers were identified. Notably, one outlier in the healthy control group was identified and removed from all models. Models testing cerebellar volumes were computed for only participants ages 16 years and older (detailed in Study Two). Whole brain volume, white/grey matter volumes, and thalamic volumes were also investigated as predictors of PCNB efficiency. A threshold of $p \leq .01$ was applied to assess statistical significance of the cerebellar predictors, to adjust for multiple comparisons and guard against false positive findings. If a cerebellar subregion was identified as a predictor of PCNB efficiency, the corresponding DTI metric characterizing the whole brain was added to the model (e.g., whole brain FA, MD, AD or RD), to determine if the cerebellum contributes to the cognitive outcome over and above the whole brain.

An exploratory analysis comparing MS patients with (n = 26) and without (n = 19) infratentorial lesions was examined, with the same methods as above. When a significant association was observed, a model including the group by cerebellar metric interaction was computed, to assess for a statistically significant difference in the association between MS groups. The model was as follows:

*PCNB efficiency ~ age + I(age^2) + sex + parental education + (T2 lesion volume) + cerebellar DTI metric + whole brain DTI metric + MSgroup + MSgroup*cerebellar DTI metric*

One outlier was removed from the MS group presenting with infratentorial lesions. Given the small sample in each group and the exploratory nature of this analysis, a threshold of $p < .05$ was applied to assess statistical significance.

Results

Cerebellar white matter as predictors of PCNB efficiency

In general, cerebellar white matter (FA, MD, AD, RD) did not predict PCNB efficiency in either the MS or healthy control groups. Contrarily, whole brain FA approached statistical significance in the MS group, such that an increase in FA by 0.01 was related to a 0.208 increase in PCNB z-score. (p = .018; **Figure 3**). Whole brain MD, AD, and RD approached significance, such that lower whole brain diffusivity predicted a higher PCNB z-score (p = .03 for each model). Data from cerebellar and whole brain DTI models are presented in **Table 14.** Supplemental data including cerebellar lobes are presented in **Supplemental Table 5**. In addition, in a supplemental analysis examining PCNB accuracy and response time z-scores, cerebellar white matter FA did not predict cognitive outcome in either group (**Supplemental Table 6**).

Table 14. Cerebellar white matter and whole brain DTI metrics (FA, MD, AD, RD) as predictors of PCNB composite efficiency z-score in MS patients and healthy controls (HC) (coefficients represent 1 unit change in DTI metric)

	MS (n=43)			HC (n=67)		
DTI metric	**B(SE)**	***p*[a]**	**95% CI**	**B(SE)**	***p*[a]**	**95% CI**
FA						
SCP	1.43(1.36)	.30	-1.33 to 4.20	0.63(1.29)	.63	-1.95 to 3.20

MCP	2.23(2.99)	.46	-3.84 to 8.30	-0.83(3.05)	.79	-6.94 to 5.28
White Matter Core	3.03(4.67)	.52	-6.44 to 12.51	2.16(3.89)	.58	5.61 to 9.93
Whole Brain	20.84(8.38)	.018	7.95 to 43.72	0.21(7.57)	.98	-14.92 to 15.34
MD ($10^{-3}mm^2$)						
SCP	-0.93(0.63)	.15	-2.21 to 0.34	-0.31(0.67)	.64	-1.66 to 1.03
MCP	-2.68(2.47)	.29	-7.68 to 2.34	1.84(2.69)	.50	-3.54 to 7.22
White Matter Core	-5.19(3.16)	.11	-11.59 to 1.22	1.04(3.17)	.74	-5.31 to 7.38
Whole Brain	-3.01(1.37)	.03	-5.79 to -0.23	-0.009(1.47)	.10	-2.96 to 2.94
RD ($10^{-3}mm^2$)						
SCP	-0.85(0.60)	.17	-2.07 to 0.38	-0.43(0.68)	.53	-1.79 to 0.94
MCP	-2.32(2.25)	.31	-6.88 to 2.24	1.38(2.87)	.63	-4.35 to 7.11
White Matter Core	-4.45(3.10)	.16	-10.74 to 1.85	0.19(2.99)	.95	-5.79 to 6.17
Whole Brain	-3.04(1.37)	.03	-5.82 to -0.26	-0.06(1.48)	.97	-3.01 to 2.90
AD ($10^{-3}mm^2$)						
SCP	-0.87(0.59)	.15	-2.07 to 0.34	-0.08(0.49)	.87	-1.06 to 0.89
MCP	-2.25(2.53)	.38	-7.39 to 2.88	0.58(1.62)	.72	-2.65 to 3.81
White Matter Core	-5.31(3.13)	.10	-11.67 to 1.05	1.35(2.76)	.63	-4.17 to 6.86
Whole Brain	-3.06(1.37)	.03	-5.83 to -0.28	-0.10(1.48)	.95	-3.07 to 2.87

Models adjusted for age, I(age^2), sex, parental education, and T2 lesion volume (MS models only)
Note. SCP = superior cerebellar peduncle; MCP = middle cerebellar peduncle
[a]Bold values indicate significant at $p \leq .01$

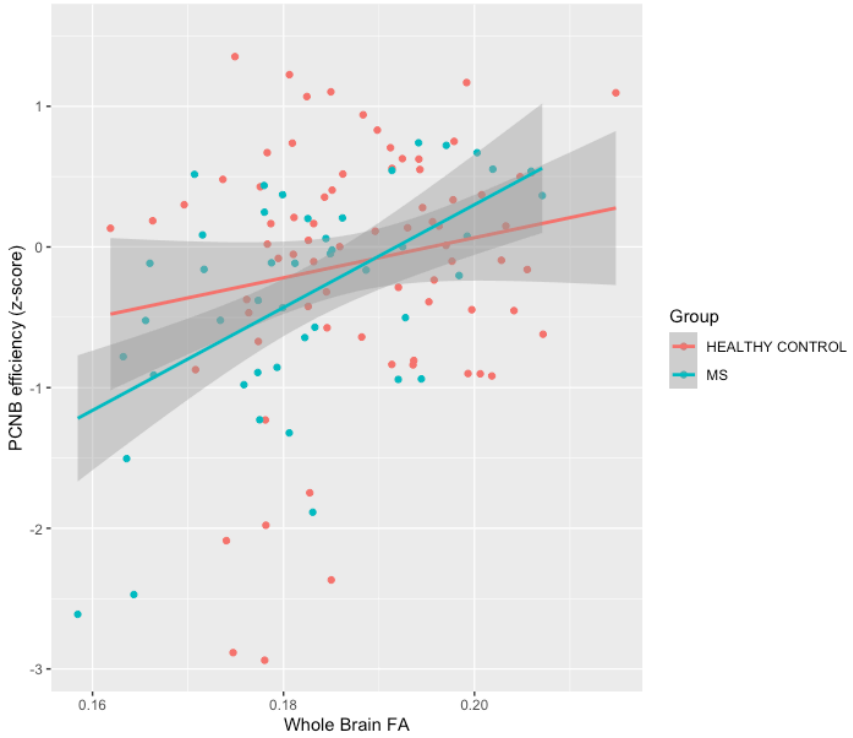

Figure 3. Scatterplot illustrating the trend for a relationship between whole brain FA and PCNB efficiency z-score in MS patients, but not in healthy controls.

Cerebellar and whole brain volumes as predictors of PCNB efficiency

Normalized volumes of cerebellar subregions did not predict PCNB efficiency z-score in either group. In addition, normalized brain (whole brain, grey/white matter) and thalamic

volumes also did not predict PCNB efficiency. Models testing normalized volumes are presented in **Table 15**. Volumes also did not predict PCNB accuracy (**Supplemental Table 7**).

Table 15. Normalized cerebellar and whole brain volumes as predictors of PCNB composite efficiency z-score in MS patients and healthy controls (HC)

	MS (n=35)			HC (n=40)		
Volume (cm^3)	**B(SE)**	***p*[a]**	**95% CI**	**B(SE)**	***p*[a]**	**95% CI**
Total Cerebellum	-0.0004(0.005)	.93	-0.01 to 0.009	0.002(0.008)	.76	-0.01 to 0.02
Anterior Lobes	0.02(0.04)	.66	-0.06 to 0.10	-0.002(0.07)	.98	-0.15 to 0.15
Posterior Lobes	-0.001(0.006)	.86	-0.01 to 0.01	0.004(0.009)	.61	-0.01 to 0.02
Cerebellar peduncles	-0.02(0.09)	.84	-0.20 to 0.20	-0.21(0.13)	.21	-0.42 to 0.10
White Matter Core	0.005(0.04)	.91	-0.08 to 0.09	-0.05(0.07)	.51	-0.19 to 0.09
Whole Brain	0.0005(0.001)	.72	-0.002 to 0.003	-0.001(0.002)	.60	-0.005 to 0.003
White Matter	-0.002(0.002)	.45	-0.002 to 0.003	-0.002(0.003)	.63	-0.008 to 0.005
Grey Matter	0.002(0.002)	.38	-0.002 to 0.003	-0.001(0.003)	.66	-0.008 to 0.005
Thalamus	-0.03(0.06)	.58	-0.002 to 0.003	0.03(0.07)	.69	-0.008 to 0.005

Models adjusted for age, I(age^2), sex, parental education, and T2 lesion volume (MS models only)
Note. All volumes normalized according to SIENAx scaling factor to adjust for head size; models computed only for participants ages 16 years and older
[a]Bold values indicate significant at $p \leq .01$

MS subgroup analysis

PCNB composite z-scores (i.e., efficiency, accuracy, response time) were compared between MS subgroups and healthy controls. Lower PCNB performance (i.e., efficiency, accuracy, response time) was noted in the MS group with infratentorial lesions ($p < .05$), relative to healthy controls. In contrast, performance in MS patients who did not present with infratentorial lesions did not statistically differ from healthy controls (**Table 16**). Notably, MS subgroups did not differ statistically with respect to PCNB z-scores.

Table 16. Differences in PCNB composite outcomes between MS patients (IT lesions present/absent) and healthy controls (HC). Means(*SD*) are presented

					IT			nIT		
PCNB outcome	**nIT (n=22)**	**IT (n=32)**	**HC (n=99)**	**Intercept**	**B(SE)**	***p***	**95% CI**	**B(SE)**	***p***	**95% CI**
Efficiency	-0.20(0.76)	-0.36(0.84)	0.00(0.86)	-6.74	-0.55(0.13)	**<.001**	-0.82 to -0.29	-0.24(0.16)	.12	-0.55 to 0.06
Accuracy	-0.06(0.54)	-0.19(0.58)	0.00(0.61)	-4.48	-0.31(0.10)	**.002**	-0.50 to -0.11	-0.05(0.12)	.66	-0.28 to 0.18
Response time	-0.15(0.55)	-0.17(0.73)	0.00(0.58)	-3.00	-0.27(0.12)	.02	-0.50 to -0.04	-0.20(0.14)	.15	-0.46 to 0.07

Models adjusted for age, I(age^2), sex, parental education. Values in bold are significant at $p \leq .01$.
Abbreviations. nIT = MS patients without infratentorial lesions; IT = MS patients with infratentorial lesions

Results of the MS subgroup regression analysis are presented in **Table 17**. With respect to the relationship between PCNB efficiency and MCP FA, a significant group by MCP interaction was observed (B(SE) = 10.32(5.00), p = .047, 95% CI = 0.14 to 20.50), indicating that MS groups statistically differed in this association. Specifically, for MS participants without infratentorial lesions, a 0.01 unit increase in MCP FA was associated with a 0.079 increase in PCNB efficiency z-score (p = .017; **Figure 4A**), when accounting for whole brain FA. In contrast, the group by MCP RD interaction only approached statistical significance (B(SE) = -8.38(4.29), p = .06, 95% CI = -17.12 to 0.35), as such the negative association between MCP RD and the PCNB z-score in the MS group without infratentorial lesions should be interpreted carefully (**Figure 4B**). The group by white matter core FA interaction was significant (B(SE) = 16.14(7.71), p = .04, 95% CI = 0.44 to 31.83). Cerebellar white matter core FA predicted PCNB efficiency in the MS group without infratentorial lesions, such that a 0.01 unit increase in white matter core FA was associated with a 0.11 increase in PCNB efficiency z-score. However, this finding only approached statistical significance when whole brain FA was included in the model (p = .053; **Figure 4C**). Finally, a significant group by white matter core RD interaction was observed (B(SE) = -12.38(6.08), p = .05, 95% CI = -24.76 to 0.002). White matter core RD predicted PCNB efficiency in the MS group without infratentorial lesions, when whole brain RD was accounted for (p = .005; **Figure 4D**), such that a 0.01 unit decrease in RD associated with a 0.14 increase in PCNB efficiency z-score. In the MS group *with* infratentorial lesions, cerebellar white matter did not predict PCNB efficiency z-score, when whole brain microstructural integrity was accounted for. Notably, total T2 lesion volume predicted PCNB efficiency z-score in both patient groups (p < .05).

Supplemental Table 8 presents the data for all cerebellar subregions. Normalized cerebellar volumes did not contribute to PCNB efficiency z-score in either MS sub-group. Similarly, normalized whole brain volume did not predict the cognitive outcome (**Supplemental Table 9**).

Table 17. Cerebellar white matter and whole brain DTI metrics as predictors of cognitive efficiency in patients with and without infratentorial lesions present.

	No IT lesions (n=18)			IT lesions (n=25)			
DTI metric	**B(SE)**	***p*[a]**	**95% CI**	**B(SE)**	***p*[a]**	**95% CI**	**Int.[b]**
FA							
SCP	1.54(1.95)	.45	-2.74 to 5.84	0.38(1.52)	.81	-2.83 to 3.59	-
MCP	8.26(3.05)	**.02**	1.55 to 14.98	-3.16(3.49)	.38	-10.52 to 4.20	-
+ whole brain	7.87(2.74)	**.017**	1.76 to 13.98	-0.69(1.85)	.71	-4.61 to 3.23	**.047**
WMC	12.68(5.42)	**.04**	0.74 to 24.62	-3.81(5.36)	.49	-15.13 to 7.51	-
+ whole brain	11.37(5.17)	.053	-0.16 to 22.90	-5.91(5.52)	.30	-17.61 to 5.78	**.04**
Whole Brain	28.82(10.45)	**.02**	5.54 to 52.10	10.28(10.28)	.33	-11.40 to 31.97	-
MD ($10^{-3}mm^2$)							
SCP	0.10(0.80)	.90	-1.65 to 1.85	-1.13(0.77)	.16	-2.76 to 0.50	-
MCP	-7.18(3.71)	.08	-15.34 to 0.99	-1.59(2.86)	.58	-7.62 to 4.43	-
WMC	-8.59(4.87)	.11	-19.30 to 2.12	-1.38(3.57)	.70	-8.91 to 6.16	-
Whole Brain	-2.15(2.39)	.39	-7.41 to 3.12	-1.64(1.52)	.30	-4.87 to 1.58	-
RD ($10^{-3}mm^2$)							
SCP	-0.12(0.77)	.88	-1.81 to 1.58	-0.88(0.74)	.25	-2.44 to 0.67	-
MCP	-6.77(2.64)	**.03**	12.58 to -0.96	0.19(2.67)	.94	-5.44 to 5.82	-
+ whole brain	-8.13(2.39)	**.007**	-13.45 to -2.81	1.21(2.77)	.67	-4.67 to 7.09	-
WMC	-10.91(4.45)	**.03**	-20.70 to -1.11	-0.10(3.39)	.98	-7.26 to 7.05	-
+ whole brain	-13.99(3.96)	**.005**	-22.81 to -5.17	0.80(3.46)	.82	-6.53 to 8.13	**.05**
Whole Brain	-2.09(2.35)	.39	-7.26 to 3.07	-1.74(1.53)	.27	-4.97 to 1.49	-
AD ($10^{-3}mm^2$)							
SCP	0.60(0.81)	.48	-1.19 to 2.38	-1.09(0.67)	.12	-2.52 to 0.33	-
MCP	5.17(4.93)	.32	-5.67 to 16.02	-5.29(2.49)	**.049**	-10.55 to -0.023	-
+ whole brain	3.92(5.48)	0.49	-7.98 to 4.54	-4.90(2.69)	.09	-10.59 to 0.80	-
WMC	-1.52(4.60)	.75	-11.65 to 8.62	-4.42(3.63)	.24	-12.09 to 3.25	-
Whole Brain	-2.48(2.54)	.35	-8.07 to 3.12	-1.55(1.52)	.32	-4.76 to 1.66	-

Models adjusted for age, I(age^2), sex, parental education, and T2 lesion volume; whole brain metric added to models significant at $p < .05$; one participant in the No IT lesion group did not have parental education data

Note. IT = infratentorial; SCP = superior cerebellar peduncle; MCP = middle cerebellar peduncle; WMC = white matter core

[a]Bold values indicate significant at $p < .05$; [b]p-values indicating significant MS group by DTI metric interaction ($p < .05$)

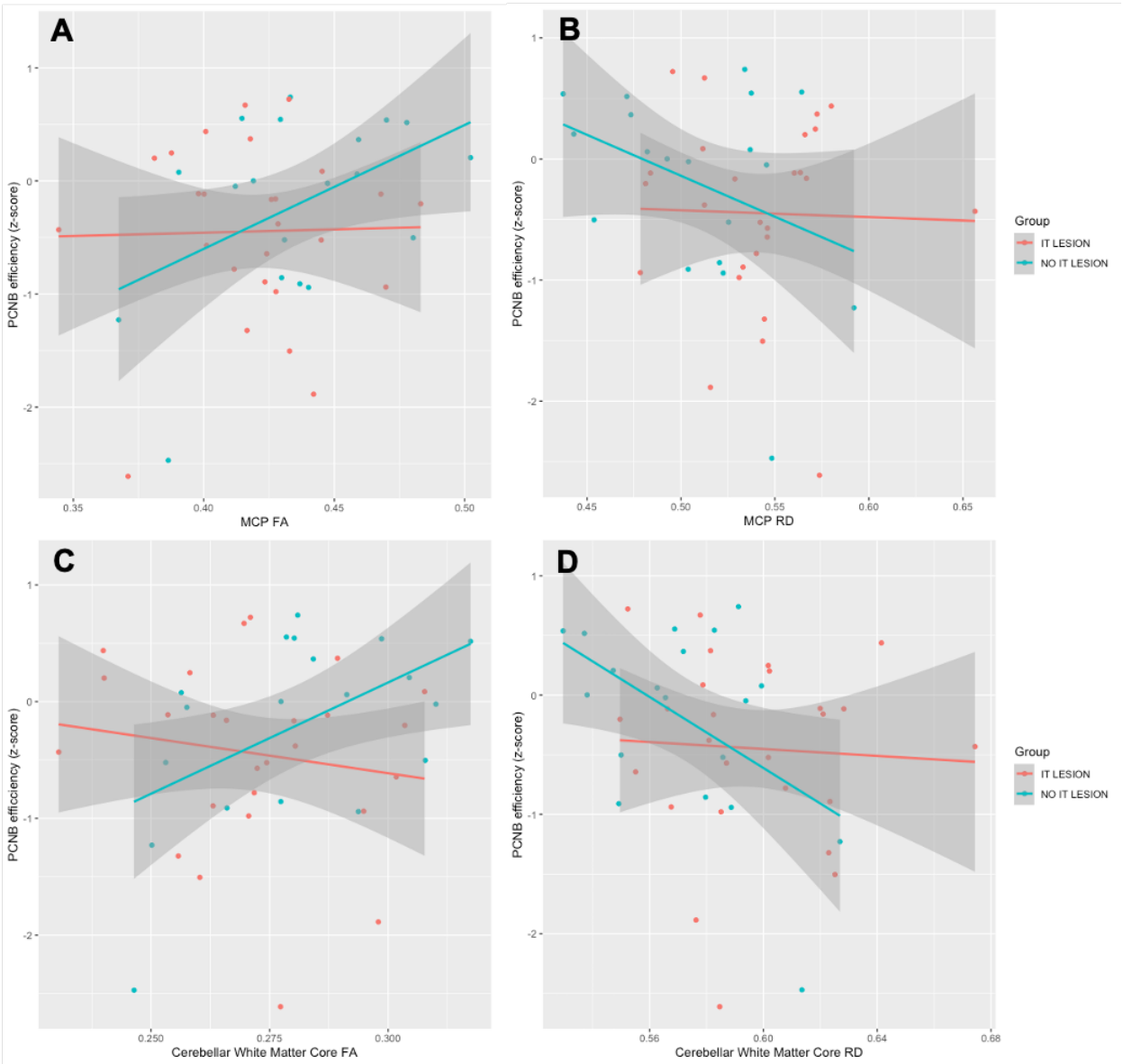

Figure 4. Scatterplots illustrating the relationship between cerebellar MCP and white matter core microstructure with PCNB efficiency z-score. A) MCP FA; B) MCP RD; C) white matter core FA; D) white matter core RD. Red indicates MS patients with infratentorial lesions; blue indicates MS patients without infratentorial lesions. Group by subregion interactions reached significance ($p<.05$) for Figures A, C, and D.

Does cerebellar white matter FA predict PCNB accuracy and/or response time?

To explore whether cerebellar white matter FA contributed more to PCNB accuracy or response time, supplemental regression models were computed (**Table 16**). Interaction terms for the group by cerebellar metric were also statistically significant for the MCP and white matter

core FA models (MCP: B(SE) = 13.81(5.28), p = .01, 95% CI = 3.06 to 24.56; White Matter Core: B(SE) = 23.58(7.99), p = .006, 95% CI = 7.31 to 39.85). Higher cerebellar MCP and white matter core FA predicted a greater response time z-score in the MS group *without* infratentorial lesions, when whole brain FA was accounted for (p = .04). Cerebellar white matter FA did not predict PCNB response time in the MS group *with* infratentorial lesions, over and above whole brain FA. No significant MS group by DTI metric interaction was noted for PCNB accuracy, and higher whole brain FA predicted higher PCNB accuracy z-score in *both* MS groups (nIT: p = .003; IT: p = .014), but did not predict response time.

Table 18. Cerebellar white matter and whole brain FA as predictors of PCNB composite accuracy and response time z-scores in MS patients with and without infratentorial lesions present

	No IT lesions (n=18)		**IT lesions (n=25)**		
DTI Metric	**B(SE)**	***p*[a]**	**B(SE)**	***p*[a]**	**Interaction[b]**
PCNB accuracy z-score					
SCP	0.45(1.55)	.78	2.00(2.04)	.34	-
MCP	2.62(3.00)	.40	3.34(4.84)	.50	-
White Matter Core	1.88(5.19)	.72	4.87(7.26)	.51	-
Whole Brain	22.88(5.66)	**.003**	32.80(12.07)	**.014**	**-**
PCNB response time z-score					
SCP	1.21(2.20)	.59	-1.86(1.82)	.32	-
MCP	8.31(3.59)	**.04**	-7.90(3.95)	.06	**.01**
+ whole brain	7.97(3.48)	**.04**	-6.32(3.98)	.13	**.01**
White Matter Core	14.96(5.83)	**.03**	-11.42(5.82)	.07	**.005**
+ whole brain	13.90(5.84)	**.04**	-9.51(6.07)	.13	**.006**
Whole Brain	18.10(14.20)	.23	-14.27(12.31)	.26	-

Models adjusted for age, I(age^2), sex, parental education, and T2 lesion volume; whole brain metric added to models significant at $p < .05$

Note. IT = infratentorial; SCP = superior cerebellar peduncle; MCP = middle cerebellar peduncle

[a]Bold values indicate significant at $p < .05$; [b]p-values indicating significant MS group by DTI metric interaction ($p < .05$)

Does sensorimotor control account for the relationship between cerebellar white matter and efficiency?

Given the well-documented role of the cerebellum in motor control, we explored the contribution of sensorimotor speed in our model. The motor praxis task was selected, as this task most appropriately reflected the motor requirements of each task (i.e., the speed of moving the mouse and selecting a response). IT and nIT groups did not statistically differ from healthy controls in their performance on this task (IT: M(*SD*) = 0.08(0.79); nIT: M(*SD*) = -0.15(0.98); HC: M(*SD*) = 0.01(0.95); **Supplemental Table 10**). Including praxis as a covariate for Study 1 analyses did not alter the group differences that were observed; however, it was noted as a statistically significant predictor of PCNB efficiency ($p < .001$; **Supplemental Table 11**). Praxis was entered into the regression models as an additional predictor (**Table 19**). When praxis was entered into the model, MCP and White Matter Core FA no longer met our statistical threshold for detecting a relationship with PCNB efficiency; however, the regression coefficients remained relatively stable. Moreover, The adjusted R^2 values decreased with praxis in the model, suggesting that this covariate did not improve the model more than would be expected by chance. Upon examining the semi-partial R^2 values, MCP FA explained 11% of the variance in PCNB efficiency when praxis was added to the model, compared to 17%. White matter core FA explained 5.8% of the variance in efficiency when praxis was accounted for, compared to 13%. As such, the contribution of white matter core FA to PCNB efficiency appeared to be more impacted by praxis performance. This is in contrast with MCP FA which continued to explain 11% of the variance in efficiency when praxis was accounted for. Overall, the impact of motor ability on cognitive performance should not be overlooked.

Table 19. Cerebellar white matter and whole brain FA as predictors of PCNB composite efficiency z-scores in MS patients with infratentorial lesions, when accounting for motor praxis performance

	No IT lesions (n=18)			No IT lesions (n=18) (praxis covariate)		
FA Metric	**B(SE)**	***p*[a]**	**R^{2b}**	**B(SE)**	***p*[a]**	**R^{2b}**
MCP	8.26(3.05)	**.02**	0.55	7.23(3.64)	.08	0.52
+ whole brain	7.87(2.74)	**.017**	0.64	7.21(3.30)	.057	0.61
White Matter Core	12.68(5.42)	**.04**	0.50	12.52(8.56)	.17	0.45
+ whole brain	11.37(5.17)	.053	0.56	11.49(8.13)	.19	0.51
Whole Brain	28.82(10.45)	**.02**	0.41	26.33(10.73)	**.04**	0.61

Models adjusted for age, I(age^2), sex, parental education, and T2 lesion volume; whole brain metric added to models significant at $p < .05$
Note. IT = infratentorial; SCP = superior cerebellar peduncle; MCP = middle cerebellar peduncle
[a]Bold values indicate significant at $p < .05$; [b]Adjusted R^2

Discussion

There is a paucity of literature examining the relationship between the cerebellum and cognitive outcomes in pediatric-onset MS, with only one study noting an association between cerebellar posterior lobe volume and tasks of information processing speed and vocabulary. To date, the contribution of cerebellar microstructure to cognitive functioning in pediatric-onset MS has not been explored. The purpose of Study Three was to address this gap in the literature. In summary, within the healthy control group and the full MS sample, neither cerebellar microstructure nor volume predicted PCNB efficiency. However, when the MS sample was stratified by the presence/absence of infratentorial lesions, cerebellar microstructure predicted efficiency. Specifically, within the MS subgroup *without* infratentorial lesions, higher MCP and cerebellar white matter core microstructure predicted a higher PCNB efficiency z-score. This relationship appeared to be driven by PCNB response time. Interestingly, patients who presented *with* infratentorial lesions did not demonstrate an association between cerebellar white matter and PCNB outcomes. The implications of these findings are briefly discussed.

In contrast with Weier et al. (2016), who noted a relationship between higher cerebellar posterior lobe volume and cognition pediatric-onset MS patients, this study did not observe any contributions of cerebellar volume to our cognitive outcome. There are several potential reasons for this discrepancy. First, in the current study, we were not able to include normalized cerebellar volumes in participants under 16 years of age, due to methodological concerns with the normalization process (described in Study Two Methods). As such, our sample size for the cerebellar volumetric analysis was significantly reduced (n = 35), and may not have provided sufficient power to detect a relationship. Second, the mean disease duration in our patient sample was approximately 3 years, in contrast with the sample in Weier et al. (2016) which had a mean disease duration of 4.6 years. In light of these findings, it is possible that the relationship between cognition and cerebellar volume presents itself in pediatric-onset MS patients as disease duration increases.

In the current study, MS disease severity appeared to distinguish cerebellar involvement in cognitive efficiency. Patients were divided according to the presence/absence of infratentorial lesions. Notably, patients with infratentorial lesions present also demonstrated greater whole brain T2 lesion volume, higher physical disability, and a greater number of clinical attacks. These patients also performed more poorly on the PCNB relative to healthy controls. As such, patients within this group were characterized as having a more severe disease course. This finding is consistent with previous research that has noted increasing disease severity with higher infratentorial (specifically, cerebellar peduncle) lesion involvement (Preziosa et al., 2014). Interestingly, a relationship between cerebellar microstructure and PCNB efficiency was not observed in this patient group. This finding may be indicative of cortico-cerebellar disconnection, as a result of damage proximal to the cerebellum. A recent study noted lower

cerebellar FA in relapsing-remitting and secondary progressive MS, as well as functional connectivity reductions between the cerebellum and various association networks (i.e., default-mode network, frontoparietal network) in secondary progressive patients (Schoonheim et al., 2021). Despite lower cognitive performance in the MS group, lower functional connectivity did not relate to cognitive outcomes. Authors postulated that reduced connectivity in severe MS disease course, such as secondary progressive MS, contributes to a "network collapse" that impedes sufficient neural processing and results in reduced cognitive performance.

An intriguing finding from the current study is that the relationship between cerebellar microstructure and cognitive efficiency was observed only in patients without infratentorial lesions. Moreover, the association with cognitive efficiency appeared to be driven by response time, such that lower cerebellar white matter integrity of the MCP and white matter core predicted slower response time, but not accuracy. It is also worth noting that whole brain white matter microstructure predicted PCNB accuracy in both patient subgroups, but not response time. These findings support the theory that adaptive functional reorganization may contribute to maintained cognitive performance, in light of MS disease pathology (Schoonheim et al., 2010). However, in the current study, evidence of adaptive mechanisms appear to be present in patients with a milder disease course. This theory is supported by studies that have observed higher cortico-cerebellar functional connectivity in MS patients with a lower T2 lesion burden, as well as a positive association between FA and functional connectivity with normal cognitive performance (Sbardella et al., 2017). Higher functional connectivity and white matter integrity in cognitively preserved MS patients has been interpreted as a compensatory mechanism, such as up-regulation of cortical association networks, in order to maintain cognitive performance (Cruz-Gómez et al., 2014; Rocca et al., 2010; Sbardella et al., 2017). Nevertheless, the literature in this

field is quite varied, with some studies reporting that cognitively impaired patients demonstrate increased cortical functional connectivity (Schoonheim, Meijer, et al., 2015). While the current study did not assess cortico-cerebellar functional connectivity among MS patients, based on the dichotomous findings between patient-subgroups, it is possible that white matter microstructural associations with cognitive efficiency may be a proxy for maintained functional connectivity of cortico-cerebellar networks. This theory will be elaborated upon in the general discussion.

Summary of Study Three Findings

A gap in the literature exists with respect to exploring how the cerebellum contributes to cognitive outcomes in pediatric-onset MS, despite a modest body of literature noting this relationship in adult-onset patients. Study Three is the first of its kind to provide evidence of an association between cerebellar white matter microstructure and cognition in this patient population. Notably, this relationship appears to be contingent on the presence of infratentorial lesions. In patients who do not present with infratentorial lesions, the cerebellum predicts cognitive efficiency. We postulate that this relationship is a result of adaptive functional reorganization in light of supratentorial MS pathology. In contrast, patients who present with infratentorial lesions showed reduced cognitive efficiency and did not demonstrate a relationship between the cerebellum on this cognitive outcome. We suggest that MS patients within this more severe subgroup demonstrate cortico-cerebellar disconnection as a result of increased lesion burden in the whole brain, as well as proximal to the cerebellum. The implications of these suggested theories will be elaborated upon further in the General Discussion.

Chapter 5: General Discussion

Summary of Findings

The purpose of this study was to determine how changes in cerebellar microstructure effect cognitive efficiency in pediatric-onset multiple sclerosis. Three studies were conducted to achieve this overarching aim. In Study One, cognitive efficiency was observed to be reduced in pediatric-onset MS patients, relative to healthy controls, on a computerized neurocognitive battery. Notably, this result appeared to be driven by patients with infratentorial lesions. In Study Two, MS participants with infratentorial lesions were identified as having reduced cerebellar microstructure in the posterior cerebellum, the MCP, and the cerebellar white matter core, relative to healthy controls. Patients without infratentorial lesions demonstrated cognitive outcomes and cerebellar microstructure that did not differ statistically from healthy controls. In Study Three, the contribution of cerebellar white matter microstructure on cognitive efficiency was explored. Contrary to expectations, results demonstrated that only in MS patients *without* infratentorial lesions did cerebellar white matter microstructure (specifically, the MCP and white matter core) predict cognitive efficiency. This result appeared to be driven by PCNB response time, as opposed to accuracy. MS patients *with* infratentorial lesions did not show an association between cerebellar white matter microstructure and cognitive efficiency. This discussion begins first by highlighting how the presence of infratentorial lesions characterized a subgroup of MS patients with greater disease severity. Subsequently, theories for the dichotomous results between patient groups will be explored, including the impact of cerebellar neural reserve on cortico-cerebellar connectivity, and the potential for cortico-cerebellar network collapse in pediatric-onset MS patients with increasing disease severity.

The presence of infratentorial lesions distinguishes MS patients based on disease severity

The presence of infratentorial lesions was consistent with markers of greater disease severity in our patient group. Patients who presented with infratentorial lesions also demonstrated higher whole brain T2 lesion volume, greater physical disability (i.e., EDSS score) and a greater number of clinical attacks, relative to the patient group that did not present with infratentorial lesions. Notably, these two patient groups did not differ statistically with respect to disease duration or age at onset. Moreover, patients with infratentorial lesions demonstrated lower PCNB performance (efficiency, accuracy, and response time z-scores) relative to healthy controls, whereas no group difference was noted between patients without infratentorial lesions and the control group.

A recent consensus paper outlined parameters requiring further investigation for their potential association with more aggressive disease course in MS; one such parameter included infratentorial lesions (Iacobaeus et al., 2020). In adult-onset MS, infratentorial and supratentorial T2 lesion volumes have been positively associated (Prosperini et al., 2011). Moreover, the presence of two or more infratentorial lesions has been shown to predict long-term disability (i.e., progression to an EDSS score of 3) in adult-onset MS following a median follow-up period of 8.7 years (Minneboo et al., 2004). In pediatric-onset MS, the accumulation of infratentorial lesions has been associated with increased disease activity (i.e., brain volume loss and higher ventricular cerebrospinal fluid) over 2-year follow-up (Bartels et al., 2019). As such, while infratentorial and supratentorial T2 lesion burden are associated, the presence of infratentorial lesions may be related to a more severe disease course. Patients with infratentorial lesions comprised 57.8% (26/45) of MS patients in our study sample. This proportion is moderately lower than previous research in pediatric-onset MS that has noted infratentorial lesions in 68-

75% of patients (Ghassemi et al., 2014; Waubant et al., 2009). Previous studies have observed greater infratentorial lesion volume and lesion count in pediatric-onset MS patients, relative to adult-onset patients matched for disease duration (Ghassemi et al., 2014; Waubant et al., 2009). These studies have investigated pediatric patients with a relatively earlier mean age of onset than participants in the current study (11.0 vs. 14.9 years, respectively). This may account for the lower proportion of patients with infratentorial lesions observed herein, as some studies have suggested that the cerebellum is more vulnerable to atrophy prior to mid-adolescence when cerebellar myelination reaches peak maturity (De Meo et al., 2019). Indeed, a study examining cerebellar and brainstem lesions in a sample with comparable age of onset (i.e., 14.4 years) observed similar proportions of cerebellar and brainstem lesion involvement (51 and 55%, respectively) (De Meo et al., 2019).

The presence of infratentorial lesions may be a sensitive marker for disease severity in MS. As noted previously, one study observed that infratentorial lesion count was the best predictor of physical disability in adult-onset patients (Minneboo et al., 2004). This is consistent with previous literature that has noted associations between infratentorial atrophy and increased physical disability (i.e., EDSS) (Edwards et al., 1999; Hickman et al., 2001). A growing body of literature has noted that increasing disability strongly associates with cerebellar-specific atrophy, such as dentate nucleus T2 hypointensity (Tjoa et al., 2005), cerebellar lesion volume (Calabrese et al., 2010; Damasceno et al., 2014; Weier, Eshaghi, et al., 2015), and MCP T2 lesion volume (Anderson et al., 2011). Specifically, the extent of cerebellar peduncle T2 lesions (MCP and SCP specifically) appears to distinguish adult-onset MS patients with higher disability (i.e., EDSS score ≥ 4) from those presenting with low physical disability (Preziosa et al., 2014). In summary,

the potential negative impact that infratentorial lesion involvement may have in pediatric-onset patients cannot be understated, given the well-documented negative outcomes in adult-onset MS.

Cerebellar microstructure is more sensitive than cerebellar volume in distinguishing patients with severe MS pathology

Contrary to our expectations, we did not detect a statistical group difference between patient groups and healthy with respect to normalized cerebellar volumes. These findings are mixed in both the pediatric and adult MS literature. In adult-onset MS, some studies have noted reduced cerebellar grey matter (Calabrese et al., 2010; Moroso et al., 2017; Weier et al., 2012) and white matter volumes (Ramasamy et al., 2009), and others have demonstrated no difference in structural cerebellar metrics between relapsing-remitting (RRMS) patients and healthy controls (Anderson et al., 2011). Some studies only observe reduced cerebellar volumes in more severe MS subtypes, such as progressive MS (Anderson et al., 2011; D'Ambrosio et al., 2017), or in patients presenting with cerebellar dysfunction (i.e., ataxia) (Anderson et al., 2009). One study in pediatric-onset MS noted failure of age-expected growth of the cerebellum, as well as reduced cerebellar volumes (Weier, Fonov, et al., 2015). The current study findings are consistent with Weier et al. (2016), who noted no difference in cerebellar volumes between pediatric-onset MS patients and healthy controls. As such, the impact of MS pathology on cerebellar volume remains to be fully elucidated in pediatric-onset MS.

Reduced microstructural MRI metrics in the posterior cerebellum and the MCP were more sensitive than cerebellar volumetrics in distinguishing MS patients from healthy controls. FA was the most sensitive DTI metric in detecting these group differences; however, higher MCP RD values suggest that demyelination may contribute to reduced white matter microstructure in the cerebellar peduncles (Sbardella et al., 2013). Interestingly, the between-

group differences in cerebellar posterior lobe and MCP microstructure appeared to be driven by the MS group that presented with infratentorial lesions. This is consistent with previous literature that has noted an association between cerebellar T2 lesions and reduced FA of the cerebellar peduncles (Hannoun et al., 2018; Tobyne et al., 2018). In contrast, cerebellar and whole-brain microstructure did not statistically differ between patients without infratentorial lesions and healthy controls, indicating that microstructural integrity may provide another useful marker of disease severity among MS patients, in addition to infratentorial lesion burden.

Previous research has demonstrated associations between worse cerebellar DTI parameters and balance deficit in adult-onset MS (Prosperini et al., 2013, 2014). Moreover, some studies comparing MS subtypes have noted reduced MCP FA in patients with primary progressive MS, compared to healthy controls and RRMS patients, and spared MCP microstructure in RRMS (Anderson et al., 2011). Notably, cerebellar FA reductions have been associated with measures of disease severity in RRMS, such as higher EDSS, longer disease duration, reduced white to grey matter ratio (Deppe et al., 2016), and higher whole brain T2 lesion load (Preziosa et al., 2014).

Beyond clinical outcomes of physical disability, a growing body of literature has explored cerebellar microstructural associations with cognitive outcomes in MS. The cerebellum is now regarded as having a vital role in cognition, with recent studies noting that cortical association networks are represented in over 80% of the cerebellar surface area (Marek et al., 2018). The current study demonstrated that, only in MS patients without infratentorial lesions, cerebellar white matter microstructure (specifically, the MCP and white matter core) predicted cognitive efficiency. This result appeared to be driven by PCNB response time, as opposed to accuracy, highlighting the cerebellum's modulatory role in cognition. Unlike previous work in

pediatric-onset MS, cerebellar volume did not predict cognitive performance (Weier et al., 2016b). In the current study, normalized volumes were only analyzed in a small subsample of patients, due to concerns with the normalization procedure on pediatric brains. As such, we may not have had sufficient power to observe a relationship between cerebellar volume and PCNB outcomes.

In contrast to cerebellar microstructure, PCNB accuracy was predicted by whole brain microstructure in both patient groups. This is consistent with previous literature that has noted associations between cognitive performance and cortical microstructure (i.e., corpus callosum) in pediatric-onset MS (Till, Deotto, et al., 2011; Todorow et al., 2014). In summary, the current study findings suggest that the cerebellum is particularly relevant with respect to modulating information processing speed, but that its modulatory role is maintained only in patients with preserved cerebellar white matter microstructure. MS patients who presented with infratentorial lesions did not show an association between cerebellar white matter microstructure and cognitive efficiency. However, whole brain microstructure predicted accuracy. Given that these patients were characterized as having a more severe disease course, we would have anticipated the cerebellum-cognition association to be present.

In the following section, mechanisms for Study Three findings are explored. Specifically, it is proposed that patients without infratentorial lesions have preserved cerebellar white matter microstructure, allowing patients in this group to maintain efficient cortico-cerebellar communication and cognitive efficiency. In contrast, patients who presented with infratentorial lesions experience pathology in proximity to the cerebellum, as well as greater whole-brain lesion burden overall. These pathological processes may contribute to cerebellar microstructural abnormalities in tracts receiving afferents from the cortex (i.e., MCP), resulting in disrupted

cortico-cerebellar information transfer. The following discussion will suggest that cortico-cerebellar disconnection and reduced network efficiency may be contributing to the lack of association between the cerebellum and cognitive efficiency in patients with more severe disease pathology.

Cerebellar microstructural abnormalities do not predict cognitive efficiency in pediatric-onset MS patients with severe disease pathology: Theories postulated

In developmental studies of healthy youth, cerebellar white matter and peduncles reach complete maturation (i.e., adult levels) in mid-adolescence (Simmonds et al., 2014). Some studies suggest that the cerebellum may be an overlooked region of the brain that contributes to cognitive maturation and neurodevelopment, given its protracted white matter development in adolescence (Marek et al., 2018). In pediatric-onset MS, lesions proximal to the cerebellum (i.e., infratentorial lesions) may negatively impact cerebellar white matter maturation, and subsequently, cognitive maturation, given that MS pathology occurs in conjunction with neurodevelopmental processes. Contrarily, in cases where infratentorial lesions are absent, cerebellar white matter maturation and its role in cognitive functioning may be somewhat spared. As such, higher cognitive efficiency was predicted by greater cerebellar microstructure only in patients without infratentorial lesions, who also demonstrated spared cognitive performance and white matter integrity relative to healthy controls.

Pediatric-onset MS patients frequently present with infratentorial lesions at onset (Alroughani & Boyko, 2018). Specifically, greater involvement of the brainstem (i.e., pons) relative to the cerebellum has been observed (Callen et al., 2009; Ghassemi et al., 2014). Nevertheless, the brainstem contributes to cortico-cerebellar circuitry via the pons (Kelly & Strick, 2003), and as such, both brainstem and cerebellar infratentorial lesion involvement may

have implications for cognitive outcomes. In the current study, patients with infratentorial lesions demonstrated poorer cognitive efficiency, relative to healthy controls and MS patients without infratentorial lesions. Despite lower efficiency scores observed, patients without infratentorial lesions did not differ statistically from healthy controls. In the following section, we postulate that differences in cerebellar structural reserve and cortico-cerebellar connection provide a theoretical basis for the dichotomous findings between patient groups.

Cerebellar reserve vs. cortico-cerebellar disconnection

Reserve is a well-studied heuristic that has been developed to explain how individual differences contribute to resilience against brain disease. There are three constructs that are currently used to describe reserve-related processes. These include: cognitive reserve, brain reserve, and brain maintenance (Stern et al., 2020). *Cognitive reserve* relates to functional capacity and adaptability that may explain individual differences in cognitive susceptibility to disease pathology. Cognitive reserve is a dynamic construct, and can be influenced by differences in innate/biological (e.g., in utero, genetic) and environmental exposures across the lifespan (e.g., education, physical activity, etc.). In light of pathology, cognitive reserve may influence how effectively a person can cope with disease-related brain changes, such as compensatory processes to maintain cognitive functioning. *Brain/structural reserve* is a fixed construct that refers to individual differences in structural characteristics of the brain (i.e., numbers of neurons, synapses). That is, higher brain reserve may allow some individuals to better cope with pathology, as increased structural capacity may protect against rapid cognitive decline. Finally, *brain maintenance* refers to the process of reducing the impact of pathology-related brain changes, and is based on genetics and lifestyle factors. The construct of brain

maintenance is predicated on the notion that the brain is modifiable based on experience, and is typically studied longitudinally.

Within the current study sample, patient differences in cerebellar structural reserve may partially account for the contrasting results observed. That is, despite experiencing MS pathology, MS patients who did not present with infratentorial lesions also presented with a less severe disease course. These patients appeared to have spared cerebellar structural reserve, evidenced by cerebellar white matter microstructure that is indistinguishable from healthy controls. As a result, patients were able to perform as controls on our measure of cognitive efficiency. In this patient group demonstrating reserve, we propose that the cerebellum may maintain its role in cognitive efficiency through preserved cortico-cerebellar connections. The MCP is known to receive feedforward afferents from the cortex via the pons, carrying information to the cerebellum (Nicoletti et al., 2017). We suggest that patients without infratentorial lesions demonstrated preserved white matter integrity of this tract that is essential in relaying motor, cognitive, and limbic information to the cerebellum. Indeed, studies that stratify MS patients by cognitive impairment have observed less extensive disruption to cerebellar white matter and cortico-cerebellar network integrity in cognitively preserved patients (Bozzali et al., 2013; Mesaros et al., 2012; Savini et al., 2019), suggesting that less severe pathology to the cerebellum may contribute to relatively maintained cognitive processing.

The literature suggests a “vertical reorganization” of cognitive functioning in the brain, such that subcortical structures (e.g., the cerebellum, among others) *modulate* cognitive processes in association with the cortex (Koziol & Budding, 2009). In support of this theory, Marek et al. (2018) observed that cerebellar BOLD signals in healthy individuals temporally lagged cortical BOLD signals, and that this latency was more pronounced for cortical association

areas (e.g., default mode, frontoparietal networks), in contrast with motor networks. As such, the cerebellum may represent the "final destination" for signals that propagate through cortical networks, which are then processed by the cerebellum and relayed back to the cortex (Marek et al., 2018). In MS, many cognitive tasks have been shown to associate with both cortical and subcortical brain regions, providing further evidence for the vertical organization of cognitive processing in this patient population (Matías-Guiu et al., 2018).

Evidence for the modulatory role of the cerebellum in cognition has been observed in MS, such that cerebellar volume tends to associate with tasks that are time-dependent and/or require precise adjustments to perform accurately (e.g., SDMT, Trail Making Test, Stroop Task, Judgement of Line Orientation) (Matías-Guiu et al., 2018; Weier, Penner, et al., 2014). As such, the cerebellum may play a particularly important role in modulating cognitive operations on tasks with time constraints. In addition, studies of cerebellar microstructure in MS have observed associations with information processing speed and working memory (Moroso, Ruet, Lamargue-Hamel, Munsch, Deloire, Coupé, Charré-Morin, et al., 2017; Schoonheim et al., 2021). Cerebellar peduncle microstructure has also been noted as one of the most important variables for classifying physically impaired and unimpaired adults with MS (Preziosa et al., 2014).

In patients *with* infratentorial lesions, structural damage occurs in proximity to the cerebellum, thereby reducing brain reserve. Given the cerebellum's known reciprocal connections with the cortex (Marek et al., 2018), it is unsurprising that this patient group that demonstrated reduced cerebellar microstructure, particularly in the MCP and white matter core, also demonstrated cognitive disruption. Processes that require increased modulation and control, such as cognitive flexibility, error detection, and attention are heavily reliant on cerebellar circuitry and are vulnerable to changes in cerebellar microstructural integrity (Rubia et al., 2007).

Lower white matter integrity in patients with infratentorial lesions may deprive participants of the cerebellum's automaticity and modulatory role, thereby resulting in poorer performance. Indeed, the cerebellum did not predict PCNB response time in this patient group, suggesting that the cerebellum does not retain its modulatory role in maintaining appropriate information processing speed (Forn et al., 2011) in patients with infratentorial damage. We hypothesize that the cerebellum loses this role as a result of cortico-cerebellar disconnection. Other disorders involving the cerebellum, such as Postoperative Posterior Fossa Syndrome, illustrate the importance of cortico-cerebellar connection to maintain cognitive function. This syndrome is a severe postoperative complication that can develop following the removal of a medulloblastoma in the posterior fossa region, and is often characterized by a loss of speech (mutism) as well as motor and cognitive deficits. Interestingly, regardless of tumour location, the principal causal factor in the development of posterior fossa syndrome is direct damage to cortico-cerebellar pathways following surgery (Patay, 2015), highlighting the essential role of cortico-cerebellar connection in cognitive processing.

In recent years, more research has investigated MS as a "multisystem disconnection syndrome," noting that disconnection of cortical and subcortical structures is likely to contribute to cognitive dysfunction in MS (Bozzali et al., 2013; Dineen et al., 2009; Mesaros et al., 2012). Given that white matter pathology in MS is distributed and multifocal (Dineen et al., 2009; Dogonowski et al., 2014), it is conceivable that disconnection affects different cognitive networks and contributes to poorer cognitive outcomes in this patient population. Indeed, tissue damage, such as demyelination or axonal degeneration, results in inefficient information transfer between brain regions due to delayed and disrupted neural signal transmission (Dineen et al.,

2009). In this vein, impaired cortico-cerebellar signal transmission may contribute to the disruption of cognitive efficiency witnessed in MS patients with infratentorial damage.

Supporting this theory, previous research has noted that lower cerebellar functional connectivity relates to cerebellar peduncle lesion load, most notably in the MCP (Dogonowski et al., 2014). This association may highlight how lesions to the cerebellar peduncles cause deficient cortico-cerebellar information transfer, resulting in reduced cerebellar functional connectivity. These findings relate to the current study, as functional connectivity has been shown to associate with white matter integrity in MS (Bozzali et al., 2013; Sbardella et al., 2017).

In patients with infratentorial lesions, cerebellar white matter microstructural reductions were noted, relative to patients without infratentorial lesions and healthy controls. RD distinguished groups more robustly than AD, suggesting that pediatric-onset MS patients with infratentorial lesions may experience greater demyelination in cerebellar white matter than axonal degeneration, contributing to cognitive and clinical disability. This finding is in line with post-mortem research that has noted demyelination and axonal preservation in cerebellar lesions (Kutzelnigg et al., 2007).

Cognitive outcomes have also been associated with cerebellar atrophy, such that cerebellar T1 lesion volume predicted information processing speed performance (Weier, Penner, et al., 2014). In cognitively impaired MS patients, substantial lesion presence in the MCP has been observed, relative to cognitively preserved patients (Tobyne et al., 2018). The presence of MCP lesions may also be related to a younger age at symptom onset, increasing the potential for cognitive dysfunction (Tobyne et al., 2018). This finding is particularly relevant to pediatric-onset MS patients, who present with greater infratentorial lesion load than adult-onset patients (Waubant et al., 2009). Nevertheless, some studies have observed disrupted cerebellar

white matter integrity (Deppe et al., 2016) and decreased glucose metabolism of the cerebellum (Derache et al., 2006) in MS patients with minimal to no cerebellar lesion involvement. As such, the cerebellum may be particularly sensitive to extra-cerebellar disease pathology, if it is unable to maintain cortico-cerebellar information transfer or to compensate for structural damage via functional reorganization.

Here we present a theory of cerebellar reserve and cortico-cerebellar disconnection as mechanisms to explain the between-group differences among patients stratified by the presence/absence of infratentorial lesions. We postulate that patients who did not present with infratentorial lesions maintained cerebellar structural reserve by way of preserved cerebellar white matter microstructure that facilitates cortico-cerebellar information transfer necessary for cognitive functioning. As these patients did not demonstrate evidence of cerebellar demyelination or axonal degeneration, these patients performed similarly to healthy controls on the PCNB. Consequently, the cerebellum uniquely predicted cognitive efficiency in this group, even when whole brain microstructure and atrophy were accounted for. The above theory provides a hypothesis for the structural mechanisms that underlie preserved cerebellar microstructure and cognitive efficiency. In the following section, we explore the functional implications of maintained cortico-cerebellar connectivity, which will also shed light on how patients in this subgroup differ from healthy controls, who did not demonstrate an association between cerebellar microstructure and cognitive efficiency.

In contrast, we hypothesize that patients who presented with infratentorial lesions were unable to maintain cerebellar structural reserve, possibly due to lesions proximal to the cerebellum, as well as an overall greater total T2 lesion burden relative to patients without infratentorial lesions. Cerebellar white matter integrity was reduced, particularly in the MCP,

which conveys associative, paralimbic, and sensorimotor afferents from the cerebral cortex. Cerebellar white matter core integrity was also reduced in this patient group, which is known to contain the dentate nuclei that serve as the cerebellum's main "relay centre" to the cortex. We suggest that this reduction in MCP and white matter core integrity may negatively impact cortico-cerebellar communication. As a result of disrupted information transfer, the cerebellum did not contribute to cognitive efficiency in this patient group. Moreover, patients were unable to compensate and maintain cognitive performance, given that they also presented with a more severe disease course (i.e., higher T2 lesion volume, higher physical disability and greater number of clinical attacks). As such, we suggest that this patient group may suffer from "network collapse" and an impaired ability for functional reorganization in light of more severe MS disease pathology. In the following section we will review theories of network efficiency and network collapse in MS.

Network efficiency vs. network collapse

The disconnection hypothesis posits that MS-related cognitive dysfunction results from white matter injury between cognitively important processing regions of the brain (Dineen et al., 2009). Indeed, studies demonstrating widespread white matter disruption in pediatric-onset MS have been noted (Akbar, Giorgio, et al., 2016). Building on this hypothesis, structural damage noted beyond lesioned areas in MS further supports a "disconnection syndrome" (Enzinger et al., 2015), particularly with respect to damage in long-range connections that are relevant in maintaining cognitive functioning (Meijer et al., 2020). As a consequence of disconnection, functional network destabilization is thought to contribute to impaired "network efficiency" and subsequent cognitive dysfunction in MS (Schoonheim, 2020; Schoonheim, Meijer, et al., 2015b).

The patient group without infratentorial lesions did not statistically differ from healthy controls with respect to cerebellar white matter integrity and cognitive efficiency; however, these groups were distinguished based on the association of the MCP and white matter core microstructure with cognitive performance. We propose that this patient group was able to compensate for MS disease processes in the supratentorium (e.g., inflammation) via adaptive functional reorganization (Schoonheim et al., 2010) and an increased reliance on cerebellar networks, in order to maintain cognitive performance. In patients with infratentorial lesions, this relationship may not be present due to reduced "network efficiency" that has taken place as a result of increased disease severity and microstructural abnormalities of the cerebellum.

Network efficiency refers to the efficiency of information transfer between brain regions (Dogonowski et al., 2014; Meijer et al., 2020) and is typically assessed by measuring the extent to which information is efficiently distributed and integrated along fibres between brain regions (Meijer et al., 2020). In MS, global (i.e., long-range) and local (i.e., short-range) reductions in white matter efficiency are observed, such that information transfer between cortical regions is reduced (Meijer et al., 2020; Shu et al., 2011). The hypothesis for network collapse postulates that, in the early stages of MS, structural damage is low, allowing for neural networks to continue functioning efficiently. As such, patients remain cognitively intact. However, as structural damage accumulates over time, networks become less efficient. Eventually, "network collapse" takes place, resulting from increasing structural damage in conjunction with declining network efficiency. After this critical threshold is reached, the network is unable to function normally and it is likely that cognitive impairment ensues (i.e., dashed line; **Figure 5**). (Schoonheim, Meijer, et al., 2015b).

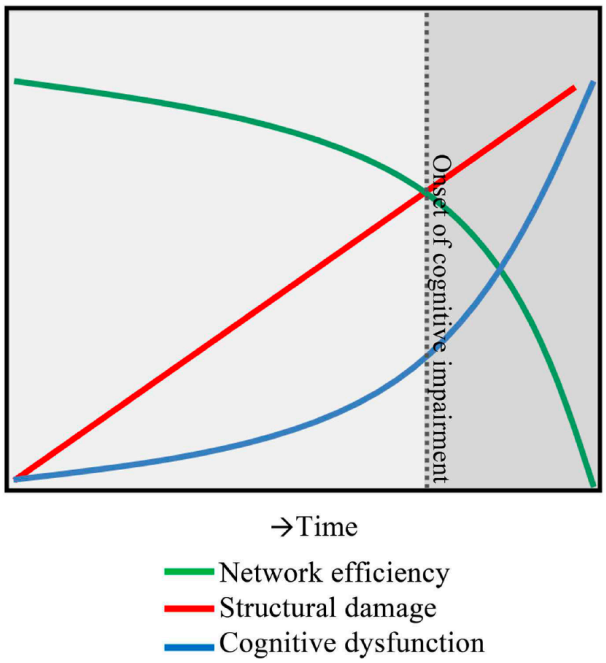

Figure 5. Network collapse hypothesis for the development of cognitive impairment in MS. Figure as published in Schoonheim et al. (2015), Front Neurol, 6:82 (with permission).

Previous research has noted associations between reduced network efficiency in MS and higher total white matter lesion load, providing evidence for disrupted network organization in the setting of increased structural damage (Shu et al., 2011). More recent work has examined the impact of MS on long- and short-range connections in the brain (Meijer et al., 2020). The brain is topographically arranged in such a way that favours short-range, "low-cost" connections (van den Heuvel & Sporns, 2013). However, a small proportion of long-range connections exist, such as the feed-forward corticopontine-pontocerebellar and feedback cerebello-thalamocortical projections (Kelly & Strick, 2003). Long-range neural connectivity facilitates rapid and efficient communication between distal brain regions (Bassett & Bullmore, 2017; Sporns & Zwi, 2004). As damage increases, long-range connections become less efficient in their ability to facilitate long-distance neural communication, and thus may have larger functional consequences (Van Den Heuvel et al., 2012), given their crucial role in integrating neural signals (Park & Friston,

2013). Meijer et al. (2020) noted reduced FA in both short- (i.e., < 75 mm) and long-range (i.e., > 158 mm) white matter connections in patients with MS, with long-range connections demonstrating the greatest reduction in microstructural integrity. Notably, authors reported that lower FA in long-range fibres associated with reduced structural network efficiency, suggesting that more severe disruption to white matter integrity related to more abnormal functional connectivity in the MS brain. Moreover, predictors of information processing speed in this study included FA of long-range connections, as well as the percentage of long-range tracts affected by white matter lesions. Similarly, in the current study, higher whole-brain T2 lesion volume predicted lower cognitive efficiency in both patient groups.

In the current study, patients with more severe disease processes demonstrate disrupted cortico-cerebellar feedforward connections by way of reduced MCP microstructural integrity. Reduced cerebellar white matter core integrity may also impact cortico-cerebellar communication via potential disruption to the deep cerebellar nuclei. Based on the existing literature, we suggest that these negative impacts on cerebellar white matter may reduce cortico-cerebellar network efficiency, and contribute to poorer cognitive performance. **Figure 6** illustrates this hypothesis.

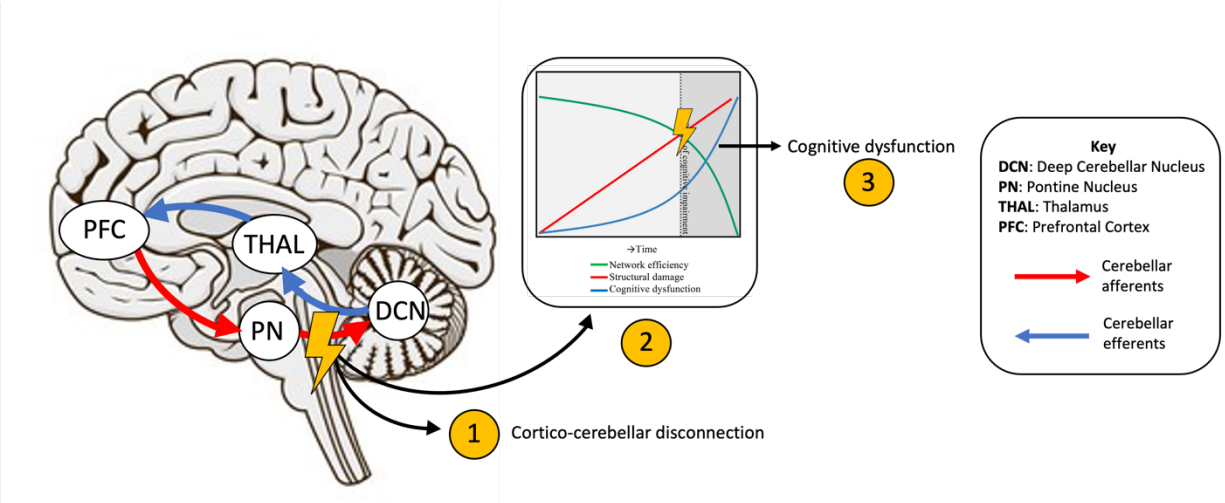

Figure 6. Illustration of cortico-cerebellar disconnection via reduced MCP and cerebellar white matter core microstructural integrity (1) and resulting decline in cortico-cerebellar network efficiency (2), contributing to poorer cognitive performance on the PCNB (3).

Because there are fewer long-range connections in the brain, they are less redundant than short-range connections and thus more vulnerable to pathology (Tononi et al., 1999). MS patients in the current study who did not present with infratentorial lesions did not demonstrate disrupted cortico-cerebellar feedforward connectivity in the MCP. Nevertheless, this group of youth presented with similar disease duration and age of onset as the patient group with infratentorial lesions. Indeed, the extent of structural damage appeared to be the major distinguishing clinical factor between patient groups.

To investigate compensatory mechanisms in cognitively preserved patients, functional connectivity studies have been employed. Importantly, functional connectivity is distinct from task-based activation, as it reflects the amount of communication between brain regions by evaluating coherent or correlated patterns of firing (Schoonheim, Meijer, et al., 2015b). Early theories hypothesized that cognitive dysfunction is delayed in MS with increasing functional reorganization in the presence of structural damage (Schoonheim et al., 2010). This was supported by a growing body of literature demonstrating increased functional connectivity in cognitively preserved MS patients, and decreased functional connectivity in cognitively impaired patients, particularly of the default-mode network. However, more recent literature has highlighted the inconsistencies in this field, as studies have demonstrated that cognitive impairment relates to both decreased (Bonavita et al., 2011; Cruz-Gómez et al., 2014; Rocca et al., 2010) and increased (Hawellek et al., 2011; Tewarie et al., 2013; Zhou et al., 2014) functional connectivity of the default-mode network in adult patients with MS (relative to healthy controls and cognitively preserved patients). In contrast, other studies note a positive

association between increased default-mode network functional connectivity and better cognitive outcomes in MS (Loitfelder et al., 2012; Wojtowicz et al., 2014).

Likewise, in pediatric-onset MS, mixed findings have been documented. Some studies have noted no difference in functional connectivity of the default-mode network between cognitively impaired and preserved patients (Rocca, Valsasina, et al., 2014). In contrast, others have observed altered functional connectivity patterns depending on cognitive status, such that cognitively impaired patients exhibit lower functional connectivity of posterior regions within the default-mode network, and cognitively preserved patients demonstrate greater functional connectivity within anterior regions of this network (Akbar, Till, et al., 2016; Rocca et al., 2014). As such, the impact of MS on default-mode network functional connectivity remains to be fully elucidated.

More consistent findings have been noted in the frontoparietal network, with increased functional connectivity noted in both adult and pediatric-onset MS patients with preserved cognitive functioning (Akbar, Till, et al., 2016; Cruz-Gómez et al., 2014; Faivre et al., 2012; Rocca, Valsasina, et al., 2014). Greater disease severity (i.e., higher lesion burden) has been postulated as a mechanism by which functional connectivity is disrupted and impacts information transmission across cognitive networks. That is, some studies have noted that adult patients with greater lesion volume demonstrate reduced functional connectivity across multiple networks (i.e., default-mode, frontoparietal, salience), relative to patients with less severe pathology (Cruz-Gómez et al., 2014; Sbardella et al., 2017).

Given that altered functional connectivity has frequently been noted in the default-mode and frontoparietal networks, an increasing body of literature in MS has examined how the cerebellum may also be implicated. The potential for cortico-cerebellar network collapse in

pediatric-onset MS has been demonstrated, with some studies observing reduced functional connectivity between the dentate nucleus of the cerebellum and cortical areas (i.e., frontal, temporal, and parietal) in cognitively impaired patients, relative to patients who are cognitively preserved (Cirillo et al., 2016). Adaptive functional rewiring has also been suggested in studies that have observed increased functional connectivity of the precuneus to the cerebellum in cognitively preserved pediatric-onset MS patients relative to healthy controls (Akbar, Till, et al., 2016). Moreover, in adult-onset MS, disrupted cortico-cerebellar functional connectivity (i.e., increased or decreased relative to healthy controls) has been associated with poorer cognitive performance (i.e., information processing speed and visuospatial memory), as well as increasing disease severity (i.e., EDSS score, total T2 lesion volume) (Bozzali et al., 2013; Cocozza et al., 2018; Pasqua et al., 2021; Sbardella et al., 2017). Notably, Pasqua et al. (2021) observed that after accounting for infratentorial lesion volume, the relationship between cortico-cerebellar functional connectivity and information processing speed was no longer present, supporting the current study hypothesis that increased lesion burden, particularly in the infratentorium, may disrupt the cerebellum's role in cognition.

In summary, altered functional connectivity within multiple networks has been associated with both decreases and increases in cognitive performance in MS. As such, the question remains regarding whether functional connectivity changes are adaptive, or maladaptive (i.e., contribute to clinical impairment). "Maladaptive functional rewiring" has been proposed as a mechanism to explain the inconsistent findings in the functional connectivity literature (Cocozza et al., 2018). The aforementioned literature suggests that functional connectivity changes are likely a combination of adaptive/maladaptive processes (Tahedl et al., 2018). That is, *domain-specific* increases in functional connectivity may improve the patient's ability to perform a cognitive

task; however, it may also disrupt performance in *domain-unrelated* tasks. For example, cognitively-preserved patients have demonstrated increased default-mode network functional connectivity relative to cognitively impaired patients (Akbar, Till, et al., 2016; Loitfelder et al., 2012; Louapre et al., 2014; Wojtowicz et al., 2014); however, functional connectivity increases in this network have also been noted in patients with upper limb motor *disability* (Zhong et al., 2017). In addition, increased functional connectivity of sensorimotor regions to the rest of the brain has been noted in patients with preserved manual dexterity (Zhong et al., 2016), whereas patients with cognitive *deficits* have also demonstrated increased functional connectivity between sensorimotor regions and the thalamus (Schoonheim, Hulst, et al., 2015). It is possible that increased functional connectivity following pathology (i.e., lesions) in domain-related networks may be an adaptive mechanism, and impaired performance on domain-unrelated tasks may be a consequence of general decreases in network communication or prioritization of the domain-related function (Tahedl et al., 2018). Simulations of MS pathology provide another hypothesis for the varying functional connectivity findings, as simulated white matter damage (constructed in a model informed by empirical data) has been shown to cause initial increases in functional connectivity, followed by global decreases (Tewarie et al., 2018). Thus, a temporal shift in functional connectivity may exist in MS, providing a rationale for future prospective studies to assess for functional connectivity changes at varying timepoints from disease onset.

Some studies have noted that structural changes in cerebellar white matter integrity (i.e., lower FA) occur in conjunction with altered cortico-cerebellar functional (Bozzali et al., 2013; Sbardella et al., 2017; Schoonheim et al., 2021) and structural (Savini et al., 2019) connectivity. As such, functional connectivity disruption may reflect underlying microstructural abnormalities in MS. In the current study, we were unable to assess cortico-cerebellar functional connectivity;

however, based on the established relationship between microstructural integrity and functional connectivity, we hypothesize that decreased network efficiency may have been observed in patients who presented with infratentorial lesions. This indeed is a major future direction for ongoing study of cortico-cerebellar connectivity in pediatric-onset MS.

Schoonheim et al. (2021) propose that increased cognitive dysfunction in more severe MS presentations (i.e., SPMS) occurs as a result of network collapse due to accumulated structural and functional damage to cortico-cerebellar connections. In their study, three patient groups were compared, including early RRMS, late RRMS, and SPMS. Notably, SPMS patients who presented with more severe pathology (i.e., higher EDSS and whole brain T2 lesion volume) also demonstrated the greatest microstructural reductions in cerebellar cortical FA and more pronounced disruption in cognitive performance, compared to the RRMS patient groups. Notably, early RRMS patients in this study demonstrated reduced cerebellar cortical FA (albeit less pronounced than late RRMS and SPMS patients) compared to healthy controls. Moreover, increased variability in functional connectivity between the cerebellum and cortical association networks was noted in all patient groups relative to controls. Changes in functional connectivity variability are thought to reflect network instability resulting in impaired information processing abilities (Vanhaudenhuyse et al., 2010). In the current study, patients with infratentorial lesions were characterized as having greater T2 lesion burden and reduced cerebellar microstructural integrity, relative to patients who did not present with infratentorial lesions. According to the network collapse hypothesis, higher structural damage, as suggested by greater lesion burden and lower cerebellar microstructural integrity, may contribute to reduced cortico-cerebellar network efficiency and disrupted cognitive efficiency in this patient group. In patients without infratentorial lesions, who presented with less structural damage overall, we postulate that

network efficiency is relatively spared, and as such, cognitive performance is maintained. Accumulating lesion burden and declining microstructural integrity may result in eventual network collapse in both patient groups.

Study limitations and future directions

While the use of a computerized cognitive battery provided advantages with respect to measuring response time in conjunction with performance accuracy, some limitations exist. Namely, the PCNB was developed with an American normative sample; given that our sample was 70% Canadian, we did not use American norms. Moreover, normative data of the child version of the PCNB has been collected for 8 to 21-year-olds. The current study administered the PCNB in youth up to age 29, further limiting our ability to use normed data. As such, the quadratic effect of age was included in each model to adjust for potential ceiling effects. Finally, we were unable to aggregate efficiency scores into their PCNB domains, due to poor fit in the MS sample as noted in a confirmatory factor analysis (data not shown). As such, future research should investigate the psychometric properties of the PCNB in pediatric-onset MS.

The use of DTI metrics as the primary structural outcome in this study has some limitations. Importantly, DTI parameters are indirect measures of microstructural integrity, as white matter content is inferred based on the extent of water diffusion in a given voxel (Soares et al., 2013). Results should therefore be interpreted with caution, as DTI metrics lack specificity with respect to white matter microstructure. That is, they may reflect various microstructural properties, including myelination, fibre coherence, axonal packing, or axonal diameter (Bruckert et al., 2019). As such, future research should combine DTI metrics with other neuroimaging techniques that assess myelin content (Laule et al., 2008), axonal diameter (Assaf et al., 2008), and crossing fibres (Zhang et al., 2012). In addition, we were unable to confidently measure

microstructural integrity of the cerebellar lobules, given the pitfalls of quantifying diffusivity in regions with tightly folding fibres and multiple tissue types (Deppe et al., 2016). The major assumption of DTI analysis is that a single diffusion tensor is sufficient to describe each voxel (Assaf & Pasternak, 2008). Within each 2x2x2 mm^3 voxel of the cerebellar lobules, there are likely thousands of axons and a single diffusion tensor may not be representative of them all. As such, in anatomically heterogenous regions like the cerebellar lobules, where white/grey matter and tightly folded/crossing bundles may exist in a given voxel, the risk of confounding diffusivity measurements (termed "partial volume effects") is extreme (Van Hecke et al., 2016b). Some studies have noted that diffusion parameters are more suitable for modelling tracts with a single dominant orientation (e.g., the corpus callosum) (Gunnarsson, 2014). Due to these methodological limitations, the current study focused on cerebellar white matter (i.e., cerebellar peduncles and white matter core) as the primary outcome of interest. Future studies should investigate cortico-cerebellar connectivity using more sophisticated neuroimaging methods that compliment and build upon structural integrity measures. Examples include functional connectivity measures of network efficiency through graph analysis (Schoonheim, Meijer, et al., 2015b), as well as complementary white matter imaging techniques that have been identified as appropriate in MS research, such as anatomical connectivity mapping (Bozzali et al., 2013). Indeed, network metrics have been shown to better capture MS-induced structural abnormalities (i.e., grey/white matter damage), and outperform non-network based MRI measures in the prediction of disability (i.e., EDSS) (Pardini et al., 2014, 2015).

In addition, we were unable to analyze volumes from all patients in the current sample, due to methodological concerns with the normalization method on pediatric (i.e., younger than 16 years) scans. As such, our sample was significantly reduced for our volumetric comparisons,

which may have impacted our power to detect differences between patients and healthy controls on normalized whole brain, grey and white matter volumes.

This study is also cross-sectional in nature, and as such, the progression of cerebellar microstructural integrity and cognitive efficiency in either patient group is unknown. Longitudinal studies are required to elucidate the long-term cognitive sequelae of cerebellar structural damage and network collapse in pediatric-onset MS. Indeed, a growing body of literature has highlighted that pediatric-onset patients reach irreversible physical and cognitive disability as well as progressive course at a younger age than adult-onset MS patients (Maria P. Amato et al., 2014; Renoux et al., 2007; Simone et al., 2002). Given that pediatric-onset patients have greater infratentorial lesion burden compared to adults (Weier et al., 2016a), as well as failure of age-expected cerebellar maturation (Weier, Fonov, et al., 2015), the long-term consequences of structural damage and impaired development of this understudied brain region is needed. While longitudinal studies examining cortico-cerebellar connections are limited, some functional neuroimaging work has shown promise with respect to increased cerebellar recruitment following 10-week cognitive rehabilitation in RRMS (Sastre-Garriga et al., 2011), as well as sustained fronto-cerebellar connectivity over one-year follow-up in early RRMS patients that related to low levels of clinical disability (Fleischer et al., 2020).

In summary, the contribution of cortico-cerebellar connectivity to cognitive performance in pediatric-onset MS remains highly unexplored. Future studies should investigate this relationship using more sophisticated neuroimaging methods that allow for measurements of network efficiency, and longitudinal studies should be conducted to determine how cortico-cerebellar network integrity contributes to cognitive outcomes over time. The cerebellum may be a region of particular utility for neurorehabilitation in MS, as the benefits of increased focus and

task awareness as well as compensatory strategies for maintaining cognitive performance following cerebellar injury have been noted in the literature (Schmahmann, 2010). Moreover, recent studies report behavioural improvement after cerebellar stimulation in cases of epilepsy, stroke, and Parkinson's disease (Miterko et al., 2019).

Concluding remarks

The use of DTI in the assessment of clinically relevant white matter tracts in patients with MS contributes to our understanding of MS pathology and the clinical implications of the disease. In pediatric-onset MS, the impact of cerebellar pathology on cognition remains to be elucidated. Damage to critical white matter tracts, such as the cerebellar peduncles, may play a major role in the accrual of cognitive dysfunction in this patient population, due to their reciprocal connections with the cerebral cortex. The current study aimed to investigate cerebellar microstructural contributions to cognitive efficiency in pediatric-onset MS. We noted that microstructural abnormalities in the cerebellum were driven by patients with infratentorial lesions, relative to patients without infratentorial lesions and healthy controls. The presence of infratentorial lesions appeared to categorize MS patients according to disease severity. We suggest that patients *with* infratentorial lesions did not demonstrate an association between cerebellar microstructure and cognitive efficiency due to disrupted neuronal conduction in cortico-cerebellar pathways supporting cognition, termed "network collapse." Further, we postulate that patients *without* infratentorial lesions demonstrated this association due to milder disease burden and intact cortico-cerebellar connectivity, contributing to sustained network efficiency. Current research in MS emphasizes network disconnection as a mechanism for cognitive dysfunction. While DTI constitutes a sensitive tool for evaluating the integrity of cortico-cerebellar networks, further research is essential to uncovering the functional

mechanisms by which pediatric-onset MS patients compensate for, or fail to adapt to, disease pathology. Future work should continue to investigate the structural and functional contributions of cerebellar networks to clinical presentation in pediatric-onset MS, as this remains un under-studied brain region, despite its pathological involvement in this patient population.

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Appendices

Appendix A. Efficiency Score vs. BIS Mathematical Proof

Example data: Line Orientation Task
$Z_{PC} = 1.66$
$Z_{RT} = 0.16$

BIS formula: $Z_{PC} - Z_{RT}$
BIS = 1.66 – 0.16
BIS = 1.50

Efficiency formula: $Z_{PC} + Z_{RT}*(-1)$
Efficiency = 1.66 + 0.16*(-1)
Efficiency = 1.66 – 0.16
Efficiency = 1.50

Appendix B. Supplemental Tables

Supplemental Table 1. Sites with available neurocognitive assessment data

Site	MS Patients Assessed (N)	HCs Assessed (N)
Alberta Children's Hospital	1	0
Children's Hospital of Philadelphia	17	35
The Hospital for Sick Children	36	73
Montreal Children's Hospital	5	0
Children's Hospital at London Health Sciences Centre	5	0
Trilium Health Partners	1	0
Janeway Children's Health and Rehabilitation Centre	1	0
Winnipeg Health Sciences Centre	2	0
Total	**68**	**108**

Supplemental Table 2. Demographics and clinical characteristics in MS participants with and without MRI analysis. Data are means (*SD*), unless otherwise specified.

	n	MRI Analyzed (n=45)	n	No/Unused MRI (n=23)	*p*	Cohen's *d*
Age at testing (yrs; mean, range)	45	17.58(8-27)	23	19.57(10-26)	.08	0.51
Sex (female:male, %female)	45	35:10 (77.8)	23	14:9 (60.9)	.24[b]	-
Participant education (years)	45	11.20(2.88)	23	12.74(3.40)	.07	0.5
Parental education (years)	43	14.12(1.98)	23	14.54(1.92)	.40	0.22
Socioeconomic status	27	34.43(15.81)	9	40.83(15.18)	.30	0.41
Emotional Distress (#normal:high, %high)	34	21:13 (38.2)	20	11:9 (45)	.84[b]	-
Participant Fatigue (median; range)						
Parent-rated	43	68.06(1.39-100)	20	62.82(33.33-100)	.75[c]	0.03
Participant-rated	44	63.20(26.39-98.61)	22	62.5(30.56-97.22)	.62	0.14
Age at disease onset (years; median, range)	45	15.07(7.32-17.86)	23	15.32(6.28-17.73)	.75[c]	0.12
Disease Duration (months; median, range)	45	16.33(3.94-133.95)	23	36.63(0.82-132.93)	.29[c]	0.44
EDSS (median, range)	45	1.5 (0-3)	23	1.5 (0-3)	.53[c]	0.17

Number of attacks (median; range)	45	2 (1-7)	23	1 (1-11)	.61[c]	0.16

Note. All p values reflect Welch's t-tests, unless otherwise specified; EDSS = Expanded Disability Status Scale; Socioeconomic status measured by the Barratt Simplified Measure of Social Status
[b]Chi-square test; [c]Mann Whitney-U test; Values in bold are significant at $p \leq .05$.

Supplemental Table 3. Demographic characteristics in healthy control participants with and without MRI analysis. Data are means (*SD*), unless otherwise specified.

	n	**MRI Analyzed (n=45)**	n	**No/Unused MRI (n=23)**	***p***	**Cohen's *d***
Age at testing (yrs; mean, range)	75	16.93(8-29)	33	17.27(10-26)	.72	0.07
Sex (female:male, %female)	75	48:27 (64.0)	33	26:7 (78.7)	.19[b]	-
Participant education (years)	75	10.92(4.38)	33	11.61(3.83)	.42	0.16
Parental education (years)	68	14.98(2.33)	31	15.48(2.08)	.28	0.22
Socioeconomic status	52	42.03(15.65)	18	45.64(13.65)	.36	0.24
Emotional Distress (#normal:high, %high)	62	41:21(33.4)	24	18:6 (25.0)	.59	-
Participant Fatigue (median; range)						
Parent-rated	59	90.28(45.83-100)	21	84.72(45.83-100)	.13[c]	0.48
Participant-rated	72	75(43.06-100)	26	72.22(13.89-95.83)	.46	0.2

Note. All p values reflect Welch's t-tests, unless otherwise specified; Socioeconomic status measured by the Barratt Simplified Measure of Social Status; [b]Chi-square test; [c]Mann Whitney-U test; Values in bold are significant at $p \leq .05$.

Supplemental Table 4. Differences in normalized cerebellar and regional brain volumes (cm^3) in MS patients with infratentorial lesions compared to patients without infratentorial lesions. Data are means (*SD*), unless otherwise specified.

Volumes (cm^3)	**nIT (n=14)**	**IT (n=21)**	**B(SE)**	***p***	**95% CI**
Total Cerebellum	181.71(23.67)	180.85(16.88)	-3.72(7.30)	.61	-18.62 to 11.19
Anterior Lobe	18.33(2.77)	18.55(1.98)	-0.42(0.89)	.64	-2.23 to 1.39
Posterior Lobe	138.55(18.25)	137.60(13.65)	-2.92(5.67)	.61	-14.50 to 8.66
Cerebellar peduncles	9.37(1.24)	9.35(0.93)	-0.18(0.39)	.65	-0.98 to 0.62
White Matter Core	15.46(2.31)	15.36(2.02)	0.24(0.82)	.77	-1.44 to 1.92
Normalized Whole Brain	1560.91(63.79)	1571.46(73.15)	-12.20(26.51)	.65	-67.36 to 38.77
Normalized Grey Matter	860.15(50.61)	847.26(62.14)	18.05(20.56)	.39	-23.88 to 59.98
Normalized White Matter	704.03(53.53)	724.02(36.48)	-29.05(16.15)	.08	-61.97 to 3.88
Normalized Thalamic	14.50(1.70)	13.89(1.92)	0.57(0.66)	.39	-0.77 to 1.92

Note. Models adjusted for age and sex; Bold indicates $p \leq .01$; IT = infratentorial lesions present; nIT = infratentorial lesions absent

Supplemental Table 5. Cerebellar and whole brain DTI metrics (FA, MD, AD, RD) as predictors of PCNB composite efficiency z-score in MS patients and healthy controls (HC)

	MS (n=43)			HC (n=67)		
DTI metric	**B(SE)**	***p*[a]**	**95% CI**	**B(SE)**	***p*[a]**	**95% CI**
FA						
Total Cerebellum	3.31(6.56)	.62	10.00 to 16.62	-1.73(8.05)	.83	-0.30 to 22.27
Anterior Lobes	10.84(7.49)	.16	-4.35 to 26.03	-6.57(7.42)	.38	-21.41 to 8.26
Posterior Lobes	-4.24(6.85)	.54	-18.13 to 9.65	-3.08(8.28)	.71	-19.64 to 13.48
Cerebellar Peduncles	2.61(2.25)	.25	-1.96 to 7.19	0.66(2.21)	.76	-3.60 to 4.92
SCP	1.43(1.36)	.30	-1.33 to 4.20	0.63(1.29)	.63	-1.95 to 3.20
MCP	2.23(2.99)	.46	-3.84 to 8.30	-0.83(3.05)	.79	-6.94 to 5.28
White Matter Core	3.03(4.67)	.52	-6.44 to 12.51	2.16(3.89)	.58	5.61 to 9.93
Whole Brain	20.84(8.38)	.018	7.95 to 43.72	0.21(7.57)	.98	-14.92 to 15.34
MD ($10^{-3}mm^2$)						
Total Cerebellum	-2.87(1.62)	.09	-6.17 to 0.42	-2.30(1.85)	.22	-5.99 to 1.39
Anterior Lobes	-2.20(0.95)	.03	-4.12 to -0.28	-0.84(0.99)	.40	-2.82 to 1.13
Posterior Lobes	-1.51(1.87)	.42	-5.30 to 2.28	-4.00(2.22)	.08	-8.45 to 0.45
Cerebellar Peduncles	-1.88(1.16)	.11	-4.23 to 0.46	-0.31(1.18)	.80	-2.67 to 2.05
SCP	-0.93(0.63)	.15	-2.21 to 0.34	-0.31(0.67)	.64	-1.66 to 1.03
MCP	-2.68(2.47)	.29	-7.68 to 2.34	1.84(2.69)	.50	-3.54 to 7.22
White Matter Core	-5.19(3.16)	.11	-11.59 to 1.22	1.04(3.17)	.74	-5.31 to 7.38
Whole Brain	-3.01(1.37)	.03	-5.79 to -0.23	-0.009(1.47)	.10	-2.96 to 2.94
RD ($10^{-3}mm^2$)						
Total Cerebellum	-2.65(1.61)	.11	-5.91 to 0.61	-2.36(1.92)	.22	-6.19 to 1.47
Anterior Lobes	-2.14(0.95)	.03	-4.07 to -0.22	-0.76(1.01)	.46	-2.78 to 1.27
Posterior Lobes	-1.26(1.87)	.51	-5.05 to 2.53	-3.85(2.26)	.09	-8.38 to 0.67
Cerebellar peduncles	-1.70(1.10)	.13	-3.93 to 0.52	-0.58(1.24)	.64	-3.06 to 1.91
SCP	-0.85(0.60)	.17	-2.07 to 0.38	-0.43(0.68)	.53	-1.79 to 0.94
MCP	-2.32(2.25)	.31	-6.88 to 2.24	1.38(2.87)	.63	-4.35 to 7.11
White Matter Core	-4.45(3.10)	.16	-10.74 to 1.85	0.19(2.99)	.95	-5.79 to 6.17
Whole Brain	-3.04(1.37)	.03	-5.82 to -0.26	-0.06(1.48)	.97	-3.01 to 2.90
AD ($10^{-3}mm^2$)						
Total Cerebellum	-3.28(1.63)	.052	-6.59 to 0.03	-2.08(1.66)	.22	-5.40 to 1.24
Anterior Lobes	-2.31(0.93)	.02	-4.20 to -0.42	-0.96(0.92)	.31	-2.81 to 0.89
Posterior Lobes	-1.93(1.85)	.30	-5.67 to 1.82	-3.95(2.11)	.07	-8.17 to 0.28
Cerebellar peduncles	-1.66(1.08)	.13	-3.86 to 0.53	-0.04(0.81)	.96	-1.65 to 1.57
SCP	-0.87(0.59)	.15	-2.07 to 0.34	-0.08(0.49)	.87	-1.06 to 0.89
MCP	-2.25(2.53)	.38	-7.39 to 2.88	0.58(1.62)	.72	-2.65 to 3.81
White Matter Core	-5.31(3.13)	.10	-11.67 to 1.05	1.35(2.76)	.63	-4.17 to 6.86
Whole Brain	-3.06(1.37)	.03	-5.83 to -0.28	-0.10(1.48)	.95	-3.07 to 2.87

Models adjusted for age, I(age^2), sex, parental education, and T2 lesion volume (MS models only)
Note. SCP = superior cerebellar peduncle; MCP = middle cerebellar peduncle
[a]Bold values indicate significant at $p \leq .01$

Supplemental Table 6. Cerebellar white matter and whole brain FA as predictors of PCNB composite accuracy and response time z-scores in MS patients and healthy controls (HC)

	MS (n=43)			HC (n=67)		
DTI Metric	**B(SE)**	***p*[a]**	**95% CI**	**B(SE)**	***p*[a]**	**95% CI**
PCNB accuracy z-score						
SCP	1.58(1.25)	.21	-0.95 to 4.11	1.00(0.95)	.30	-0.91 to 2.90

MCP	3.69(2.71)	.18	-1.80 to 9.18	3.81(2.22)	.09	-0.64 to 8.26
White Matter Core	4.85(4.25)	.26	-3.76 to 13.47	4.00(2.90)	.17	-1.80 to 9.81
Whole Brain	24.22(7.31)	**.002**	7.53 to 39.95	11.32(5.45)	.04	0.43 to 22.22
PCNB response time z-score						
SCP	-0.13(1.24)	.92	-2.65 to 2.39	-0.38(1.15)	.74	-2.68 to 1.92
MCP	-0.47(2.70)	.86	-5.95 to 5.02	-3.96(2.67)	.14	-9.32 to 1.39
White Matter Core	-0.08(4.22)	.98	-8.63 to 8.47	-2.45(3.46)	.48	-9.38 to 4.47
Whole Brain	-1.61(8.14)	.84	-18.12 to 14.90	12.52(6.56)	.06	-25.65 to 0.59

Models adjusted for age, I(age^2), sex, parental education, and T2 lesion volume (MS models only)
[a]Bold values indicate significant at $p \leq .01$;

Supplemental Table 7. Normalized cerebellar and whole brain volumes as predictors of PCNB composite *accuracy* z-score in MS patients and healthy controls (HC)

	MS (n=35)			**HC (n=40)**		
Volume (cm^3)	**B(SE)**	***p***	**95% CI**	**B(SE)**	***p***	**95% CI**
Total Cerebellum	-0.001(0.005)	.84	-0.01 to 0.009	-0.001(0.005)	.84	-0.001 to 0.01
Anterior Lobes	0.02(0.04)	.71	-0.07 to 0.10	0.006(0.05)	.90	-0.10 to 0.11
Posterior Lobes	-0.003(0.006)	.65	-0.02 to 0.010	-0.0007(0.006)	.90	-0.01 to 0.01
Peduncles	0.01(0.09)	.90	-0.17 to 0.19	-0.06(0.09)	.51	-0.23 to 0.12
White Matter Core	0.04(0.04)	.38	-0.05 to 0.13	-0.03(0.05)	.59	-0.12 to 0.07
Whole Brain	0.0001(0.001)	.93	-0.003 to 0.003	-0.001(0.001)	.46	-0.004 to 0.002
White Matter	-0.002(0.002)	.41	-0.003 to 0.003	-0.002(0.002)	.42	-0.004 to 0.002
Grey Matter	0.001(0.002)	.56	-0.003 to 0.003	-0.001(0.002)	.62	-0.004 to 0.002
Thalamus	0.03(0.06)	.59	-0.003 to 0.003	-0.01(0.05)	.78	-0.004 to 0.002

Models adjusted for age, I(age^2), sex, parental education, and T2 lesion volume (MS models only)
Note. All volumes normalized according to SIENAx scaling factor to adjust for head size; models computed only for participants ages 16 years and older

Supplemental Table 8. Cerebellar subregion and whole brain DTI metrics as predictors of PCNB efficiency in MS patients with and without infratentorial (IT) lesions

	No IT lesions (n=18)			**IT lesions (n=25)**		
DTI metric	**B(SE)**	***p*[a]**	**95% CI**	**B(SE)**	***p*[a]**	**95% CI**
FA						
Total Cerebellum	13.06(8.48)	.15	-5.61 to 0.32	-2.44(8.13)	.77	-19.61 to 14.71
Anterior Lobe	10.92(10.75)	.33	-12.74 to 34.58	10.85(9.37)	.26	-8.92 to 30.62
Posterior Lobe	8.75(9.72)	.39	-12.64 to 30.14	-8.51(9.02)	.36	-27.54 to 10.52
Cerebellar Peduncles	5.17(2.98)	.11	-1.38 to 11.72	-0.25(2.41)	.92	-5.34 to 4.84
SCP	1.54(1.95)	.45	-2.74 to 5.84	0.38(1.52)	.81	-2.83 to 3.59
MCP	8.26(3.05)	**.02**	1.55 to 14.98	-3.16(3.49)	.38	-10.52 to 4.20
+ whole brain	7.87(2.74)	**.017**	1.76 to 13.98	-	-	-
White Matter Core	12.68(5.42)	**.04**	0.74 to 24.62	-3.81(5.36)	.49	-15.13 to 7.51
+ whole brain	11.37(5.17)	.053	-0.16 to 22.90	-	-	-
Whole Brain	28.82(10.45)	**.02**	5.54 to 52.10	10.28(10.28)	.33	-11.40 to 31.97
MD ($10^{-3}mm^2$)						
Total Cerebellum	-2.95(2.69)	.30	-8.87 to 2.97	-2.41(1.75)	.19	-6.09 to 1.28
Anterior Lobe	-1.17(1.25)	.37	-3.93 to 1.60	-2.39(1.13)	.05	-4.77 to -0.0013
Posterior Lobe	-3.69(3.44)	.31	-11.26 to 3.88	-1.36(1.95)	.50	-5.48 to 2.77
Cerebellar Peduncles	-0.31(1.63)	.85	-3.88 to 3.27	-1.81(1.32)	.19	-4.60 to 0.98
SCP	0.10(0.80)	.90	-1.65 to 1.85	-1.13(0.77)	.16	-2.76 to 0.50
MCP	-7.18(3.71)	.08	-15.34 to 0.99	-1.59(2.86)	.58	-7.62 to 4.43
White Matter Core	-8.59(4.87)	.11	-19.30 to 2.12	-1.38(3.57)	.70	-8.91 to 6.16

Whole Brain	-2.15(2.39)	.39	-7.41 to 3.12	-1.64(1.52)	.30	-4.87 to 1.58
RD ($10^{-3}mm^2$)						
Total Cerebellum	-2.98(2.53)	.26	-8.55 to 2.59	-2.18(1.77)	.23	-5.92 to 1.55
Anterior Lobe	-1.13(1.24)	.38	-3.86 to 1.59	-2.40(1.15)	.052	-4.82 to 0.026
Posterior Lobe	-3.80(3.46)	.30	-11.42 to 3.81	-1.14(1.96)	.57	-5.27 to 2.99
Cerebellar Peduncles	-0.95(1.51)	.54	-4.27 to 2.37	-1.25(1.26)	.34	-3.92 to 1.42
SCP	-0.12(0.77)	.88	-1.81 to 1.58	-0.88(0.74)	.25	-2.44 to 0.67
MCP	-6.77(2.64)	**.026**	12.58 to -0.96	0.19(2.67)	.94	-5.44 to 5.82
+ whole brain	-8.13(2.39)	**.007**	-13.45 to -2.81	-	-	-
White Matter Core	-10.91(4.45)	**.03**	-20.70 to -1.11	-0.10(3.39)	.98	-7.26 to 7.05
+ whole brain	-13.99(3.96)	**.005**	-22.81 to -5.17	-	-	-
Whole Brain	-2.09(2.35)	.39	-7.26 to 3.07	-1.74(1.53)	.27	-4.97 to 1.49
AD ($10^{-3}mm^2$)						
Total Cerebellum	-2.56(3.05)	.42	-9.27 to 4.14	-2.81(1.67)	.11	-6.34 to 0.71
Anterior Lobe	-1.23(1.28)	.36	-4.06 to 1.59	-2.32(1.09)	**.047**	-4.62 to -0.03
+ whole brain				-2.46(1.38)	.09	-5.39 to 0.47
Posterior Lobe	-3.21(3.34)	.36	-10.56 to 4.14	-1.81(1.93)	.36	-5.89 to 2.26
Cerebellar Peduncles	1.45(1.59)	.38	-2.06 to 4.96	-2.23(1.15)	.07	-4.66 to 0.20
SCP	0.60(0.81)	.48	-1.19 to 2.38	-1.09(0.67)	.12	-2.52 to 0.33
MCP	5.17(4.93)	.32	-5.67 to 16.02	-5.29(2.49)	**.049**	-10.55 to -0.023
+ whole brain	-	-	-	-4.90(2.69)	.09	-10.59 to 0.80
White Matter Core	-1.52(4.60)	.75	-11.65 to 8.62	-4.42(3.63)	.24	-12.09 to 3.25
Whole Brain	-2.48(2.54)	.35	-8.07 to 3.12	-1.55(1.52)	.32	-4.76 to 1.66

Models adjusted for age, I(age^2), sex, parental education, and T2 lesion volume (MS models only); whole brain metric added to models significant at $p < .05$

Note. IT = infratentorial; SCP = superior cerebellar peduncle; MCP = middle cerebellar peduncle

[a]Bold values indicate significant at $p < .05$

Supplemental Table 9. Normalized cerebellar subregion and brain volumes as predictors of PCNB efficiency in MS patients with and without infratentorial (IT) lesions

	No IT lesions (n=14)			**IT lesions (n=21)**		
Volume (cm^3)	**B(SE)**	***p***	**95% CI**	**B(SE)**	***p***	**95% CI**
Total Cerebellum	0.002(0.006)	.76	-0.01 to 0.02	-0.007(0.008)	.42	-0.02 to 0.01
Anterior Lobes	0.02(0.06)	.79	-0.12 to 0.15	-0.03(0.07)	.66	-0.17 to 0.11
Posterior Lobes	0.003(0.008)	.75	-0.02 to 0.02	-0.009(0.01)	.42	-0.03 to 0.01
Peduncles	-0.01(0.12)	.92	-0.30 to 0.27	-0.13(0.14)	.38	-0.43 to 0.18
White Matter Core	0.03(0.06)	.63	-0.12 to 0.18	-0.04(0.06)	.56	-0.16 to 0.09
Whole Brain	-0.001(0.002)	.49	-0.006 to 0.003	0.002(0.002)	.21	-0.001 to 0.005

Models adjusted for age, I(age^2), sex, parental education, and T2 lesion volume (MS models only)

Note. All volumes normalized according to SIENAx scaling factor to adjust for head size; models computed only for participants ages 16 years and older

Supplemental Table 10. Differences in sensorimotor tasks between MS patients (IT lesions present/absent) and healthy controls (HC). Means(*SD*) are presented

					IT			nIT		
PCNB outcome	**nIT (n=22)**	**IT (n=32)**	**HC (n=99)**	**Intercept**	**B(SE)**	***p***	**95% CI**	**B(SE)**	***p***	**95% CI**
Motor Praxis	-0.15(0.98)	0.08(0.79)	0.01(0.95)	-4.38	-0.15(0.16)	.34	-0.47 to 0.17	-0.28(0.19)	.14	-0.65 to 0.09
Finger Tapping	-0.22(1.17)	-0.37(0.81)	0.00(1.00)	-3.89	-0.47(0.18)	.011	-0.83 to -0.11	-0.34(0.21)	.11	-0.76 to 0.08

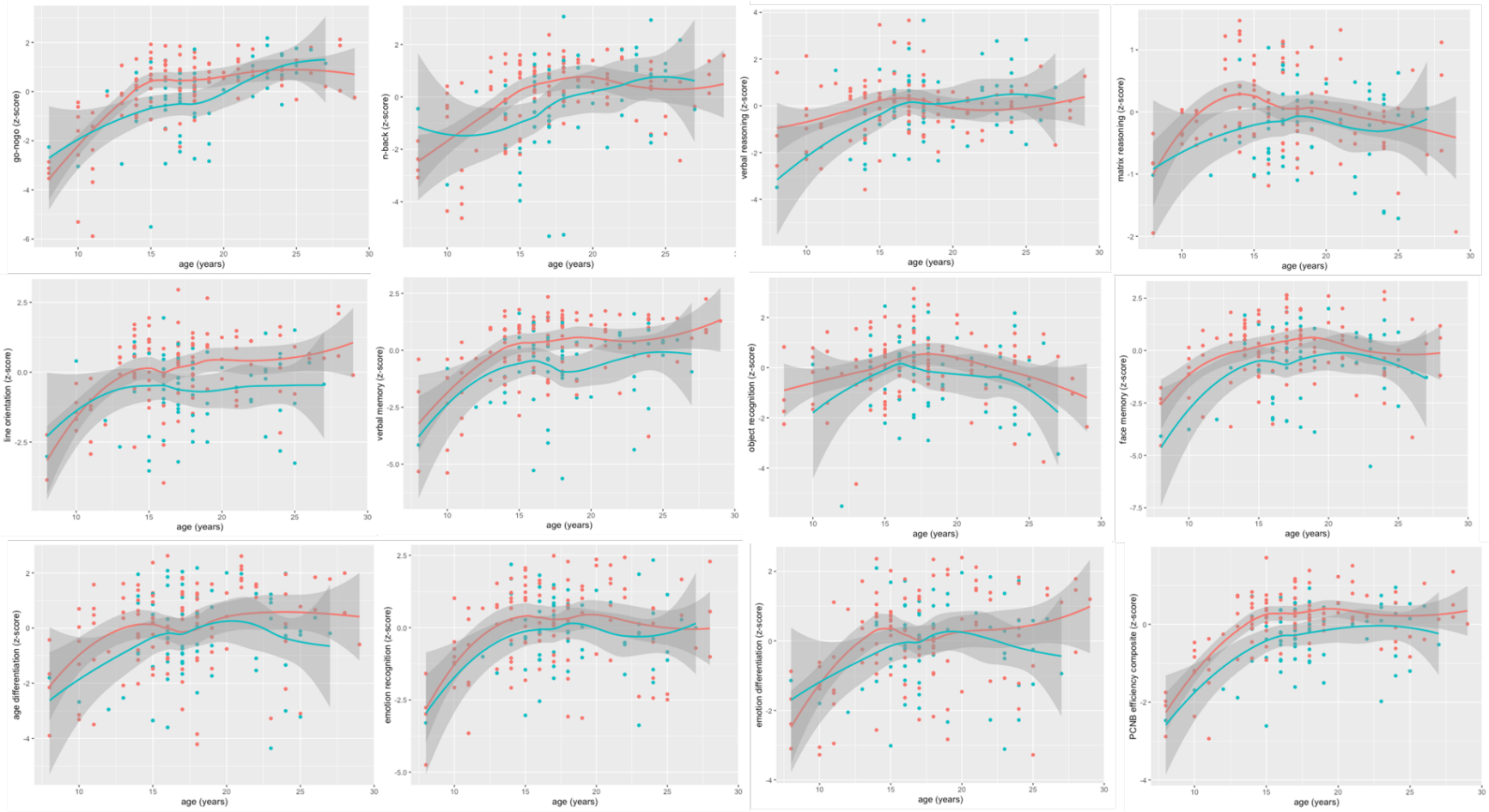
Models adjusted for age, I(age^2), sex, parental education. Values in bold are significant at $p \leq .01$.
Abbreviations. nIT = MS patients without infratentorial lesions; IT = MS patients with infratentorial lesions

Supplemental Table 11. Group differences in efficiency adjusting for motor praxis

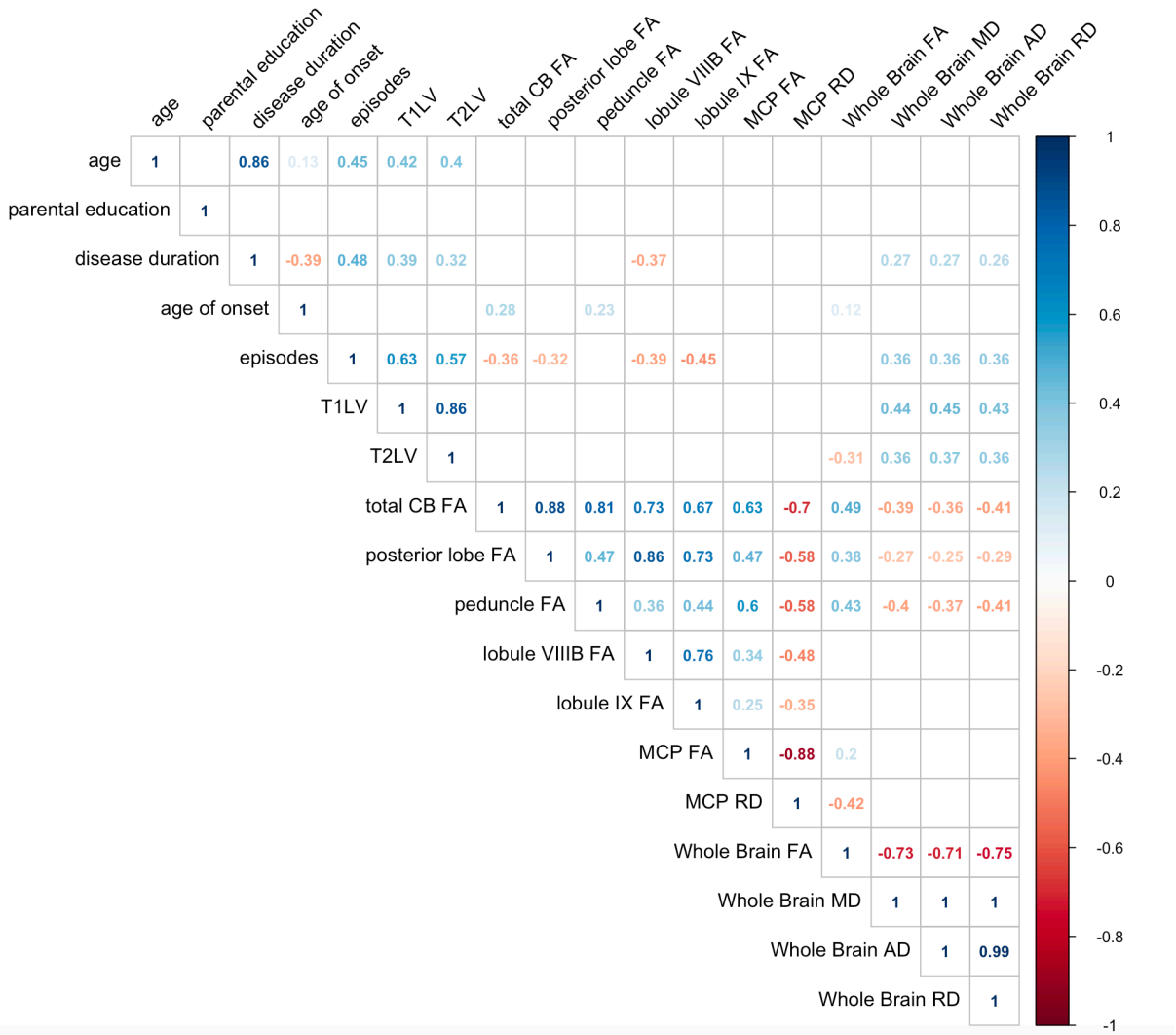
		MS		**HC**			
Test (z-score)	**n**	**M(*SD*)**	**n**	**M(*SD*)**	**B(SE)[1]**	***p***	**95% CI**
N-back	**63**	-0.23(1.73)	97	0.02(1.46)	-0.40(0.23)	.08	-0.86 to 0.06
Go-No-Go	**66**	-0.24(1.45)	99	0.02(1.49)	-0.50(0.18)	**<.001***	-0.86 to -0.14
Verbal Reasoning	**62**	-0.06(1.48)	96	-0.05(1.21)	-0.16(0.22)	.45**	-0.59 to 0.26
Matrix Analysis	**66**	-0.22(0.65)	99	0.01(0.67)	-0.21(0.11	.05*	-0.42 to 0.002
Line Orientation	**66**	-0.60(1.33)	97	0.04(1.35)	-0.62(0.20)	**.002****	-1.02 to -0.22
Verbal Memory	**66**	-0.63(1.64)	98	0.04(1.56)	-0.69(0.24)	**.004***	-1.15 to -0.22
Face Memory	**66**	-0.56(1.72)	97	0.01(1.51)	-0.63(0.25)	.012	-1.13 to -0.14
Object Memory	**65**	-0.26(1.52)	98	0.01(1.33)	-0.27(0.21)	.20**	-0.67 to 0.15
Age Differentiation	**66**	-0.27(1.59)	99	0.01(1.57)	-0.29(0.25)	.26	-0.78 to 0.21
Emotion Recognition	**65**	-0.16(0.27)	98	0.06(1.45)	-0.16(0.22)	.45*	-0.59 to 0.26
Emotion Differentiation	**66**	-0.08(1.23)	99	0.00(1.41)	-0.15(0.21)	.46*	-0.56 to 0.26
PCNB Composite	**66**	-0.31(0.82)	99	0.00(0.86)	-0.38(0.11)	**<.001*****	-0.58 to -0.17

[1]Unstandardized beta coefficients for predictor "group".
Model adjusted for age, I(age^2), sex, parental education, and motor praxis. Parental education was included in the model, and data were available for 99 HCs and 66 MS. Values in bold are significant at $p \leq .01$. Sample size differs across tests due to exclusion of invalid subtest data.

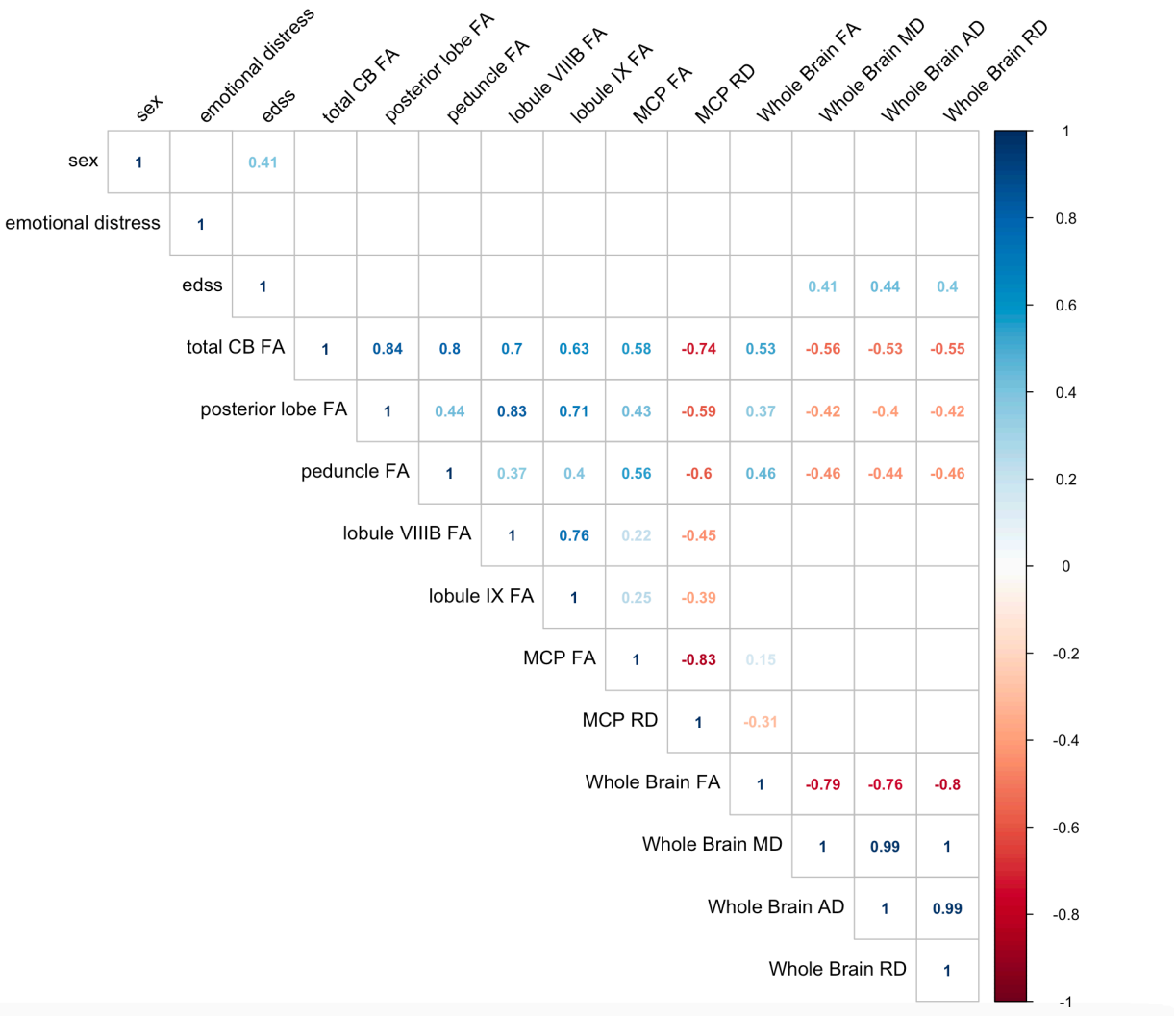
Appendix C. Supplemental Figures



Supplemental Figure 1. Plots of PCNB efficiency z-scores for each subtest and composite with age. HCs are denoted in red, MS in blue.



Supplemental Figure 2. Pearson correlation matrix in MS participants for DTI metrics that differed between groups. Numbers specify *r* values that were statistically significant at $p \leq .05$. Blank cells indicate no significant bivariate correlation.



Supplemental Figure 3. Spearman correlation matrix in MS participants for DTI metrics that differed between groups. Numbers specify *r* values that were statistically significant at $p \leq .05$. Blank cells indicate no significant bivariate correlation.