Functional Activation Patterns in Pediatric-Onset Multiple Sclerosis: Does Physical Activity Play a Role in the Maintenance of Working Memory

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Abstract

Cognitive impairment occurs in only 30% of patients with pediatric-onset multiple sclerosis (POMS), despite significant brain pathology, suggesting that mechanisms facilitating adaptation to pathology may be occurring. We examined executive control processing in 20 cognitively-preserved POMS patients and 20 age and sex-matched healthy controls, using a working memory task, while participants underwent functional neuroimaging. Participants also completed a neuropsychological battery and structural imaging in a 3T scanner. Findings suggest that inefficient processing and/or compensatory recruitment occurs in cognitively-preserved POMS patients for working memory tasks, at both low and high levels of executive demand. Strenuous physical activity had limited correlations with recruitment in POMS patients, but was predictive of whole-brain grey and white matter volume, as well as relapse rate, suggesting that engagement in aerobic activity may have a protective rather than enhancing role.

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List of Abbreviations

9HPT- Nine Hole Peg Test

AL- Alphabetize

ANOVA- Analysis of Variance

BA- Brodmann Area

BDNF- Brain-Derived Neurotrophic Factor

BSMSS- Barratt Simplified Measure of Social Status

BOLD- Blood Oxygen Level Dependent

CES-D- Center for Epidemiological Studies Depression Scale for Children

CNS- Central Nervous System

EBV- Epstein-Barr Virus

EDSS- Expanded Disability Status Scale

DICOM- Digital Imaging and Communications in Medicine

FEAT- fMRI Expert Analysis Tool

FILM- FMRIB's Improved Linear Model

FLAIR- Fluid-Attenuated Inversion Recovery

FLAME- FMRIB's Local Analysis of Mixed Effects

fMRI- functional Magnetic Resonance Imaging

FMRIB- Oxford Center for Functional MRI of the Brain

FW- Forward

GLTPAQ- Godin-Shephard Leisure Time Physical Activity Questionnaire

GM- Grey Matter

HC- Healthy Control

L- Left

MCFLIRT- Motion Correction FMRIB's Linear Image Registration Tool

MNI- Montreal Neurological Institute

MRI- Magnetic Resonance Imaging

MS- Multiple Sclerosis

NAA- N-Acetylaspartate

NIfTI- Neuroimaging Informatics Technology Initiative

PEDs-QL- Pediatric Quality of Life Inventory Multidimensional Fatigue Scale

PD- Proton Density

POMS- Pediatric-Onset Multiple Sclerosis

R- Right

RAVLT- Rey Auditory Verbal Learning Test

ROI- Region of Interest

RRMS- Relapsing Remitting Multiple Sclerosis

SES- Socioeconomic Status

SDMT- Symbol Digit Modalities Test

TMT-A- Trail Making Test part A

TMT-B- Trail Making Test part B

TE- Echo Time

TI- Inversion Time

TR- Repetition Time

VO_2max- Maximum Volume of Oxygen

WASI- Weschler Abbreviated Scale of Intelligence

WJ-III- Woodcock-Johnson-III Battery

WM- White Matter

1. Introduction

1.1 Multiple sclerosis. Multiple sclerosis (MS) is a chronic demyelinating and degenerative disease of the central nervous system (CNS) that has a prevalence rate in Canada that is among the highest worldwide (240 cases per 100 000) (Poppe, Wolfson, & Zhu, 2008). Although MS has generally been considered a disease of young adulthood, with a typical age of onset of 20-40 years old (Confavreux, Aimard, & Devic, 1980), there is increasing recognition of this disease in children and adolescents, with up to 10% of patients diagnosed prior to age 18 (Simone et al., 2002).

Though the causes of MS are still largely unknown, it is believed that there is an interaction of both genetic and environmental factors (Andalib et al., 2013). According to Belbasis, Bellou, Evangelou, Ioannidis, and Tzoulaki (2015), 44 risk factors have been studied for an association with the disease. Of these factors, exposure to the Epstein-Barr Virus (EBV) and smoking have the most consistent and significant associations with MS, however, these factors have low specificity, with up to 90% of the world's population testing positive for EBV (Cohen, 2000), and a small fraction of smokers being diagnosed with MS. Low serum vitamin D has also been considered as a contributing factor, due to the increased prevalence of MS in regions farther from the equator, however, evidence for this association is heterogeneous (Theodoratou, Tzoulaki, Zgaga, & Ioannidis, 2014). Notably, women appear to be twice as likely to be diagnosed with MS, but only following puberty, suggesting a potential role of gonadal hormones in the development of this disease (Duquette & Girard, 1993; Ghezzi et al., 1997).

The pathology of MS is characterized by focal inflammation of the myelin, which results in axonal damage and scarring (Bruck, 2005; Siffrin, Vogt, Radbruch, Nitsch, & Zipp, 2010). Neuronal loss and cell body atrophy have also been observed, and may be attributable to inflammatory responses directly, or reflect secondary degenerative effects of the damaged and unstimulated axons (Siffrin et al., 2010; Trapp & Nave, 2008). Magnetic Resonance Imaging (MRI) research has indicated that individuals with pediatric-onset MS, on average, demonstrate lower global brain volumes than healthy controls (HCs), as well as lower regional volumes in the thalamus and corpus callosum (Till et al., 2011). The involvement of these structures likely reflects the typically multifocal distribution of pathology, as each of these structures plays a central role in relaying information across the brain. Volume loss in the thalamus is particularly

notable and can occur prior to observable volume loss in whole brain metrics (Kerbrat et al., 2012; Mesaros et al., 2008).

This pattern of pathology leads to a range of both physical and cognitive symptoms that are dependent on which areas of the CNS are affected (O'Connor & Canadian Multiple Sclerosis Working Group, 2002). Though the symptoms observed within and across individuals varies substantially, MS is typically detected through the presentation of physical symptoms, such as visual problems, or numbness and/or tingling of the face, body, or extremities (Boiko et al., 2002).

The presentation of symptoms depends on the type of MS, of which there are four: Relapsing-Remitting MS (RRMS), Primary-Progressive MS, Secondary-Progressive MS, and Progressive-Relapsing MS (Weinshenker et al., 1989). RRMS is the most common subtype of MS, with up to 97% of patients with pediatric-onset showing this presentation (Boiko et al., 2002). It is characterized by unpredictable and isolated relapses, during which the new symptoms appear and existing ones worsen, followed by periods of complete or near complete recovery. Conversely, the progressive forms are characterized by an accumulation of symptoms over time, with the primary subtype occurring from onset, and the secondary subtype typically occurring 10-20 years following the diagnosis of RRMS and in approximately 50% of these individuals (Boiko et al., 2002; Weinshenker et al., 1989). Children and adolescents with MS are almost exclusively diagnosed with RRMS (Boiko et al., 2002), and the time to reach the secondary progressive stage is longer, however, this stage is ultimately met at a younger age than adults with MS (Simone et al., 2002).

1.2 Cognitive impairment. The cognitive difficulties observed in patients with pediatric-onset MS have become a subject of interest in recent years. Impairment, typically described as performance that is 1.5 standard deviations below the normal range on at least three tests, has been observed in approximately 30% of patients (Amato et al., 2008; Till et al., 2011), with both the prevalence and severity of impairment increasing as the disease progresses (Amato et al., 2010). Such deficits can be problematic in their impact on academic and intellectual abilities, as skills fail to develop at an age appropriate rate, and can be of sufficient severity to compromise future societal and vocational independence (Amato et al., 2008; MacAllister et al., 2005).

Deficits are observed in a number of cognitive functions, including attention, language, visuospatial skills, and memory; however, processing speed and executive functions, such as

working memory, seem to be particularly sensitive to MS pathology (Amato et al., 2010; Banwell & Anderson, 2005; MacAllister, Christodoulou, Milazzo, & Krupp, 2007; Till et al., 2011). Processing speed may be vulnerable due to the direct impact of MS on the myelin sheath, which is implicated in the speed of action potential propagation (Waxman, 1977). This is supported by the observation of positive correlations between processing speed and white matter (WM) integrity (Turken et al., 2008), and negative correlations between this function and WM lesion load (Duering et al., 2014).

Executive functions consist of a range of skills that are implicated in supervisory and self-regulatory control, and direct a person to engage in goal-directed behaviour (Anderson, 2002). Functions commonly included within this umbrella term are cognitive flexibility (ability to shift between mental sets), inhibition (selective attention to relevant information and inhibition of unwanted responses), goal setting (initiating, planning, and organizing a strategy), and working memory (temporary storage and manipulation of information) (Anderson, 2002; Miyake et al., 2000). These functions tend to develop more fully later in life, as adolescents complete myelination of the prefrontal cortex (De Luca & Leventer, 2008). Consequently, these functions may be sensitive to the pathological processes that occur concurrently with ongoing myelination (MacAllister et al., 2007).

Within the domain of executive functions, working memory has gained attention as a particularly prevalent deficit in MS patients (Banwell & Anderson, 2005; Till et al., 2012). Given the reliance of working memory on the coordination of distributed networks, its sensitivity may be attributable to the tendency for MS to disrupt widespread neural networks (Fuentes et al., 2012; Krupp, Banwell, Tenembaum, & International Pediatric MS Study Group, 2007). Furthermore, these deficits may be compounded by processing speed difficulties (Demaree, DeLuca, Gaudino, & Diamond, 1999).

Mixed findings have been reported on the relative risk for cognitive dysfunction posed by an earlier onset of the disease. Some studies have demonstrated that a younger age of onset is associated with greater impairment over time (Banwell & Anderson, 2005), while others have found that this relationship is no longer significant when disease duration is accounted for (MacAllister et al., 2005; Till et al., 2012). This relationship is likely complex, with children and adolescents having more active neuroplastic mechanisms, as well as fewer alternate networks established (Cramer et al., 2011; Kennard, 1942).

Risk for cognitive impairment may be heightened for adult males with MS (Beatty & Aupperle, 2002; Schoonheim et al., 2012; Schoonheim et al., 2014). Similar trends have been observed in studies of pediatric patients, however, it has yet to be determined whether increased prevalence of impairment in male youth is attributable to the greater proportion of male patients having an early onset of the disease (Amato et al., 2014; Till et al., 2011). Cognitive impairment also appears to be more prevalent in youth with comorbid mood or anxiety disorders (Weisbrot et al., 2014). Conversely, disease duration, number of relapses, and disability status have not shown consistent relationships with cognitive symptoms (Bigi & Banwell, 2012; MacAllister et al., 2007).

Although it is accepted that the damage to neural connections via inflammation is associated with some disability in MS (De Stefano et al., 1998), it is believed that the secondary neuronal loss and cell body atrophy may be the cause of the observed long-term cognitive deficits (Hoffmann, Tittgemeyer, & von Cramon, 2007; Siffrin et al., 2010). This theory is supported by Till et al. (2011), who found that neuropsychological task performance was more strongly correlated with MRI measures of brain volume than with T1 and T2 lesion volumes.

1.3 The reserve hypothesis. Despite the high lesion volume and brain atrophy observed initially across patients with pediatric-onset MS (Till et al., 2011; Waubant et al., 2009; Yeh et al., 2009), it is noteworthy that cognitive impairment is typically detected years after clinical onset (Amato et al., 2010). Although MS patients with greater lesion load and cerebral atrophy are at increased risk for cognitive impairment (Filippi et al., 2010), such correlations have been only modest, with disease burden accounting for approximately 15-30% of the variance in cognitive performance (Benedict et al., 2006; Christodoulou et al., 2003). This disconnect between disease burden and cognitive function has been observed across neurological conditions (Sumowski & Leavitt, 2013), and suggests that individual differences exist in how effectively these youth are able to withstand brain pathology.

Stern (2002) proposed a theory of brain and cognitive reserves, which posits that individuals will vary in the clinical expression of brain pathology due to differences in brain structure and function. Brain reserve is the more passive model, wherein a larger brain size and a greater number of synapses may account for differences in clinical outcomes. It is then posed that once a threshold of pathology is met, deficits will be observed. Conversely, cognitive reserve is an active model, wherein the brain attempts to compensate for pathology. This may

occur through the use of existing alternate networks or through the development of new networks (Stern, 2002, 2009).

Each of these models involves neuroplastic processes to some extent. In other words, both brain and cognitive reserves depend, in part, on the capacity of our nervous system to change. In brain reserve, neuroplasticity may play a role in healing affected brain regions. Neural growth factors have been associated with remyelination of axons after both central and peripheral injury (McTigue, Horner, Stokes, & Gage, 1998), protecting them from demyelination-associated degeneration (Irvine & Blakemore, 2008). Furthermore, neural growth factors may inhibit inflammatory processes, neurotoxicity, and apoptosis (Chen, Xiong, Tong, & Mao, 2013).

Neuroplasticity is also directly implicated in the functional differences that allow individuals to adapt to disease pathology. Throughout life, we create and strengthen networks through synaptogenesis and long-term potentiation. These mechanisms can be genetically predetermined or be mediated by environmental input, and are responsible for the existing networks that can be accessed for a particular function, as well as for the engagement of alternate networks following insult (Schinder & Poo, 2000). Importantly, such processes may eventually be exhausted, as brain pathology increases, leading to the observation of cognitive impairment (Schoonheim, Geurts, & Barkhof, 2010).

Functional Magnetic Resonance Imaging (fMRI) studies of adult MS patients support this theory, as MS patients with similar task performance to HCs show more significant and extensive brain activation than their healthy counterparts, while MS patients with cognitive impairment show less activation than those cognitively preserved (Amann et al., 2011; Mainero et al., 2004). Similar observations were described in a review by Barulli and Stern (2013). Furthermore, it was suggested that cerebral activation increases with higher levels of task demand, for those who are able to maintain task performance, while those who demonstrate cognitive difficulties show decreased activity, as the network becomes overwhelmed. The brain's limited capacity to recruit additional 'healthy' areas for functional reorganization has been referred to as the "disease progression hypothesis" and is illustrated in Figure 1 (Schoonheim et al., 2010).

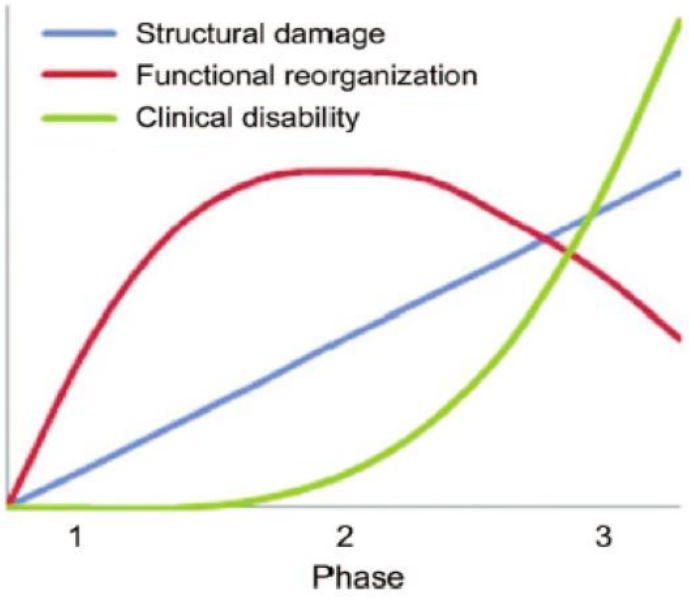

Figure 1. Multiple Sclerosis disease progression hypothesis (taken from Schoonheim et al., 2010). As shown in Phase 1, very little structural damage causes a strong response in functional reorganization and hyperactivation in the brain, resulting in low disability and cognitive preservation. In Phase 2, functional reorganization reaches its peak, and decreases in Phase 3, as cognitive impairment and disability progressively develop.

Given the noted differences in neuroplasticity in younger individuals, as well as the immaturity of neural networks, children and adolescents with MS may demonstrate different patterns in adapting to disease insult. As previously mentioned, children and adolescents with MS tend to take longer than adults to reach a secondary progressive stage, wherein symptoms no longer regress between episodes but rather accumulate over time, however, this stage is met at a younger age (Simone et al., 2002). This slower rate of disability accrual in children may reflect a lower vulnerability for CNS tissue disruption as compared with adult-onset MS and a higher regenerative capacity of the CNS. Conversely, the impact of the disease is likely deleterious to the formation of developing brain networks, leading to exhaustion of reserves at a younger age and greater cognitive difficulties in the long-term. Only long-term evaluation of pediatric-onset MS patients can elucidate the potential for greater neuroplasticity in this population.

1.4 Physical activity. Exercise, and physical activity more generally, have been gaining attention for their apparent role on brain health. Physical activity is defined as "any bodily movement produced by skeletal muscle that results in energy expenditure" (Caspersen et al.,

1985, p. 126), while exercise refers to a specific sub-category of physical activities that are "planned, structured, repetitive and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective" (Caspersen et al., 1985, p. 128).

Greater physical activity has been associated with increased brain volume and better cognitive function in both healthy and neurological populations, at a variety of developmental stages (Hotting & Roder, 2013). In a meta-analytic study of healthy older adults, it was found that fitness training increased cognitive performance by 0.5 standard deviations on average, regardless of the task, training method, or participant characteristics (Colcombe & Kramer, 2003). Although the literature tends to focus on the efficacy of aerobic exercise in improving brain function, there is also literature in support of the efficacy of physical activity in general (Huang, Larsen, Ried-Larsen, Moller, & Andersen, 2014). Notably, there is some evidence for a dose-response relationship, with greater intensity exercise leading to greater increases in the anticipated mediating factor, Brain-Derived Neurotrophic Factor (BDNF) (Ferris, Williams, & Shen, 2007).

Physical activity appears to positively affect processing speed and executive functions, including working memory (Motl, Gappmaier, Nelson, & Benedict, 2011; Ploughman, 2008), mirroring those functions which appear to be targeted by MS pathology. The largest effect sizes are demonstrated for aerobic exercise and executive functions, specifically in high demand tasks requiring cognitive control (Chaddock et al., 2012; Colcombe & Kramer, 2003; Kramer et al., 1999). This sensitivity of executive functions to exercise has been observed in children and adolescents, as well as in older adults, suggesting that this relationship is not age-dependent (Best, 2010; Davis et al., 2007; Erickson & Kramer, 2009). Notably, each of these age groups represents a period in which executive functions may be undergoing developmental changes.

In a structural neuroimaging study of adults with MS, higher fitness correlated inversely with lesion load, as well as positively with grey matter (GM) volume and WM integrity (Prakash, Snook, Motl, & Kramer, 2010). Notably, cardiovascular fitness was associated with preserved GM volume in the midline cortical structures known to show significant deterioration as a result of this disease, suggesting that physical activity may play a role in preserving structures that are vulnerable to pathological or neurodegenerative processes

In an fMRI study of working memory activation in MS patients (Prakash et al., 2007), individuals with higher cardiovascular fitness levels demonstrated greater brain activation in the

middle and inferior frontal gyrus, which were recruited by MS patients to compensate for disease burden. Additionally, lower fitness was associated with enhanced activation of the anterior cingulate, potentially reflecting a greater requirement for conflict monitoring in these individuals.

Similar activation patterns have been observed in physically active children and older adults (Colcombe et al., 2004; Davis et al., 2007). Chaddock et al. (2012) observed that higher-fit children demonstrate greater upregulation of cerebral activity than their lower-fit counterparts with increasing task demands, allowing them to maintain accuracy on the executive control task. These data suggest that the beneficial effect of physical activity may be mediated by its influence on neuroadaptive mechanisms.

A number of mechanisms have been proposed to mediate the relationship between physical activity and neurological outcomes. The predominant theory is that greater brain volumes and better cognitive functioning may be the result of an increase in the release of brain growth factors, such as BDNF, which is implicated in neurogenesis and synaptogenesis (Vaynman & Gomez-Pinilla, 2005). Notably, baseline levels of BDNF appear to differ based on age, with the highest levels occurring in mid-life (Bus et al., 2011; Bus et al., 2012), suggesting that the efficacy of physical activity interventions could differ depending on the age of the affected individual. Given the observation that the relationship between physical activity and cognitive function has been particularly strong in elderly and youth populations, it is proposed that functions undergoing developmental (or pathological) changes might benefit most from exercise interventions (Hotting & Roder, 2013).

Physical activity has been associated with increased vasculature in the brain (angiogenesis), which would improve blood perfusion to the brain, thus enhancing overall brain health (Berggren, Kay, & Swain, 2014). Increases in N-acetylaspartate (NAA), which is implicated in mitochondrial energy production and is a marker of neuronal health, have also been observed, and correlations have been shown between NAA levels, fitness, and working memory (Erickson et al., 2012). Additionally, physical activity can reduce stress, thereby minimizing the counteractive dampening of neuroplastic mechanisms by stress hormones (Salmon, 2001).

Physical activity has been associated with improvements in MS symptoms and slowing of disease progression (Hillman, Erickson, & Kramer, 2008; Motl, Dlugonski, Pilutti, Sandroff, & McAuley, 2012; Motl et al., 2010). More specifically, inverse associations have been observed

between physical activity level (both concurrent and premorbid) and changes in disability over 6 month and 24 month periods, respectively (Motl et al., 2012; Motl, Snook, Wynn, & Vollmer, 2008). Furthermore, improvements have been observed with respect to aerobic capacity and muscle strength, symptoms of fatigue and mood, walking ability, and quality of life in adults with MS (Garrett & Coote, 2009; Motl & Gosney, 2008; Snook & Motl, 2009).

Unfortunately, adults (Motl, McAuley, Sandroff, & Hubbard, 2015) and children (Grover et al., 2015a) diagnosed with MS are, on average, less active than their healthy counterparts. Frau et al. (2015) found that 38% of adults with MS ceased their engagement in physical activity with the onset of their diagnosis, however, those who were active believed that they experienced benefits as a result of being physically active. Moreover, Grover et al (2015b showed significantly lower participation in strenuous physical activity in youth with MS (n=31) in comparison to children with monophasic demyelination disease (n=79) (45.2% vs. 82.3%, p=0.0003), as determined using a 7-day activity recall questionnaire (modified Godin-Shepard Leisure Time Physical Activity Questionnaire [GLTPAQ]). MS patients did not, however, differ from controls with respect to their level of moderate or mild physical activity. Fatigue, depression, and pain are common symptoms of MS that have demonstrated relationships with patient activity level (Crayton & Rossman, 2006; Grover et al., 2015b; Krupp, 2004).

1.5 Rationale. Up to 10% of individuals with MS develop symptoms in childhood or adolescence. As compared with the adult-onset form of the disease, the corresponding literature on pediatric MS is in its early stages. Cognitive impairment has been identified as an important sequela of this disease which can impact an individual's quality of life, however, further work is required to understand the cognitive abilities most affected and the factors that play a role in limiting such impairment.

Although relationships have been demonstrated between brain pathology (ie. lesion load, brain volume loss) and cognitive function, these relationships explain only a modest proportion of the variance in cognitive function, suggesting that other mediating factors are at play. Research is needed to identify compensatory neural mechanisms, as well as what modifiable lifestyle factors may influence such mechanisms. The adult literature, as well as literature in other pathological populations, shows promise for physical activity as having beneficial effects on brain structure and function, however, these relationships require further exploration in the pediatric-onset MS population.

1.6 Objectives and hypotheses.

1. **To examine *behavioural performance* (ie. accuracy and response time) with increasing executive demand in pediatric-onset MS patients, as compared with age-matched controls.**

   Hypothesis: In the absence of cognitive impairment, pediatric-onset MS patients were expected to perform as well as controls on both the low and high demand conditions of this task.

2. **To examine the *functional activation patterns* occurring with increasing executive demand, in pediatric-onset MS patients, as compared with age-matched controls.**

   Hypothesis: Greater and more extensive activation was predicted in patients, as compared with controls, reflecting the enhanced engagement of task-related regions and recruitment of additional regions. We also hypothesized engagement of a larger neuronal network at higher levels of executive demand, as compared with the low-demand condition, in both the patient and control groups.

3. **To explore the relationship between physical activity and use of compensatory brain mechanisms in pediatric-onset MS patients.**

   Hypothesis: Level of engagement in strenuous physical activity was predicted to correlate positively with brain activation during the task, in regions recruited by MS patients.

2. Methodology

2.1 Participants. Twenty-four patients with relapsing-remitting pediatric-onset MS, and between the ages of 13-25, were recruited from the Hospital for Sick Children and by online advertisement. Twenty-seven HCs were also recruited from the web advertisement and through the Undergraduate Participant Pool at York University.

Prior to testing, participants were screened by telephone or in the clinic, to ensure that inclusion criteria were met. Patients were included if they were clinically stable at the time of evaluation and less than 4 weeks from any MS-related relapse or corticosteroid treatment. Individuals with a history of brain insult due to neurological illness or trauma, psychiatric illness, or reporting abuse of alcohol or illicit drugs were excluded. Participants were also excluded if they had braces or other magnetic implants that could cause injury in the MRI scanner or artefact in the collected images (see Appendix A for MRI safety form).

2.2 Measures

2.2.1 Demographics. Each participant completed questionnaires assessing general health (fatigue, mood), sociodemographic information, and handedness. More specifically, fatigue was assessed via the Pediatric Quality of Life Inventory Multidimensional Fatigue Scale (PEDs-QL; Varni, Seid, & Rode, 1999), mood was assessed via the Center for Epidemiological Studies Depression Scale for Children (CES-DC; Faulstich, Carey, Ruggiero, Enyart, & Gresham, 1986), and socioeconomic information was summarized using the Barratt Simplified Measure of Social Status (BSMSS; Barratt, 2006). Disease-related information was obtained from the patient health record, including: the date of their first clinical attack, age at disease onset, date of diagnosis, number of relapses, Expanded Disability Status Scale (EDSS) score, date of last EDSS score, and current medications.

2.2.2 Physical activity. Physical activity was measured using the GLTPAQ (Godin & Shephard, 1985), which has been correlated with VO_2max, a measure of maximal aerobic power, and has shown a test-retest reliability coefficient of $r = 0.81$ (Sallis, Buono, Roby, Micale, & Nelson, 1993). Based on our previous work and preliminary observations of the data, it appears that the strenuous activity subscore has greater construct validity than the total Godin score. Collaborators have found strong correlations between this subscore and accelerometry data, $r = 0.65$, $p < .001$ (Grover et al., 2015a). We will thus explore the use of this subscore as our measure of physical activity, in addition to the traditional Godin measure.

2.2.3 Neuropsychological assessment. All participants were evaluated with a battery of clinical neuropsychological tests assessing: IQ, processing speed, attention, verbal learning/memory, and executive function. Specifically, this battery includes: the Nine Hole Peg Test (9HPT; Mathiowetz, Weber, Kashman, & Volland, 1985), Rey Auditory Verbal Learning Test (RAVLT; Schmidt, 1996), 2-subscale form of the Weschler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999), Decision Speed and Auditory Working Memory tests of the Woodcock-Johnson III (WJ-III; Woodcock, McGrew, & Mather, 2001), oral administration of the Symbol Digits Modalities Test (SDMT) (Smith, 2000), and Trail Making Tests (TMT) – Parts A & B (Reitan, 1992). A similar set of tasks has been validated for detecting cognitive problems in childhood-MS (Portaccio et al., 2009). The neuropsychological battery and questionnaires were administered by trained graduate students, and took 75-90 minutes to complete.

Age- and sex-normed z-scores were calculated for each task separately, and composite scores were developed to describe general neuropsychological functioning and cognitive efficiency. The general neuropsychological composite consists of one z-score from each of the tests. The RAVLT total score and TMT B were included to represent each of these measures, and both Verbal and Performance z-scores from the WASI were included separately, to represent a range of functions and minimize redundancy for the composite. Cognitive efficiency was estimated by calculating the average of the SDMT and W-J III Decision Speed z-scores. Cognitive impairment was defined as performance 1.5 standard deviations below average on three or more subtests out of a total of 7 unique measures. Participants meeting these criteria were excluded from further analyses, given that brain activation patterns have been shown to differ between individuals with and without cognitive impairment (Mainero et al., 2004; Rocca et al., 2014).

2.2.4 Alphaspan task. While undergoing functioning neuroimaging, participants completed the Alphaspan task, which was chosen for its capacity to separate executive control processes (working memory) from storage and rehearsal processes. In this task, participants are asked to study a set of three or five consonant letter strings, and then to either maintain the letter set in the forward order (low executive demand), or to manipulate the letters into alphabetical order (high executive demand) (see Figure 2). Henceforth, these will be referred to as the "forward" (FW) and "alphabetize" (AL) conditions.

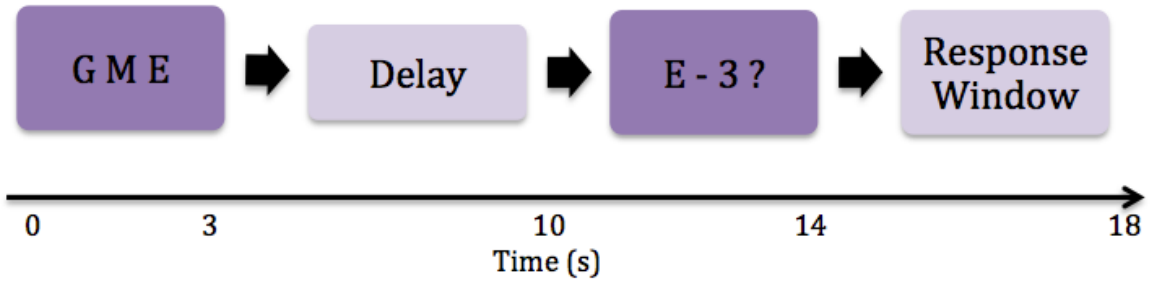

Figure 2.1 A sample "low executive demand" trial, using the 'Maintain 3' condition. Subjects respond to the cue "E-3?" (i.e. *Was E the third letter in the array*?) after a 7 second delay.

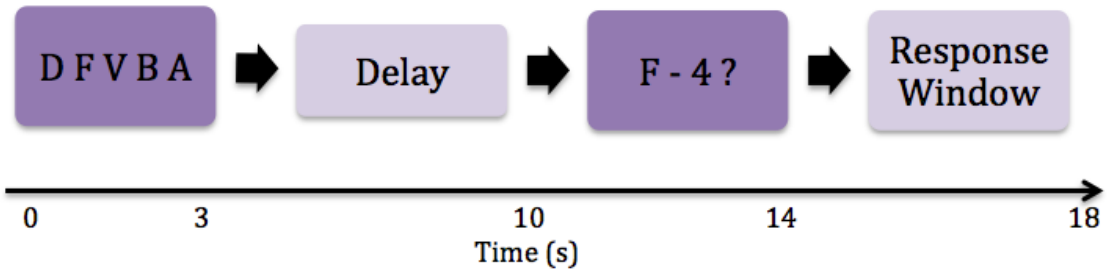

Figure 2.2 A sample "high executive demand" trial, using the 'Alphabetize 5' condition. Subjects respond to the cue "F-4?" (i.e. "*Was F the fourth letter in the alphabetized array?")* after a 7 second delay.

The task begins with a probe that informs the subject of the condition (FW or AL). Participants are then presented with the letter set (either three or five letters) for three seconds. After a seven second delay, a probe (such as 'L-3') is presented, consisting of a letter and a position, signalling "Was L the third letter in the set?" In the FW condition, the probe refers to the ordinal position; in the AL condition, the probe refers to the ordinal position after the set has been reorganized into alphabetical order. Participants were instructed to determine if the probe matches what was presented in the set, and the probability of a correct probe was set to 0.5. Participants respond with a "yes/no" button press on an MRI compatible keypad (Current Designs, CA) using their index and middle fingers of their dominant hand.

Participants completed 7 practice trials in each of the four conditions (ie. 3 and 5 letters in the FW and AL conditions) before entering the scanner. During scanning, subjects completed 12 trials of each of the task conditions. This paradigm has been validated as an fMRI probe for working memory in diffuse brain injury (Turner & Levine, 2008).

For the current analyses, set size (i.e. 3 or 5 letter string) was collapsed across condition to increase the number of trials per executive demand condition [i.e. FW (3/5 string) vs. AL (3/5 string)]. The percent of items answered correctly was calculated as a measure of accuracy, and time to respond was averaged across trials, as a measure of response time, for the FW and AL conditions.

2.2.5 Imaging procedures. Scans were carried out at the York MRI Facility on a Siemens 3.0 Tesla MAGNETOM Tim Trio scanner (Erlangen, German). Once in the scanner, participants viewed the task-related stimuli through a back projection screen (Avotec SV-6011) with angled

mirrors mounted on a 32-channel head coil. Foam padding was used to comfortably secure the participant's head in the head-coil, and to minimize head motion during scans. The total time for scanning was 70 minutes for HCs and 90 minutes for patients.

2.2.5.1 Structural MRI acquisition and processing. A high-resolution structural volumetric image was acquired from all participants using a T1-weighted three-dimensional MPRAGE sequence (1mm isotropic voxel size, Repetition Time (TR)=2300 ms, Echo Time (TE)=2.96 ms). Proton density (PD)-weighted (TR=2200 ms, TE=10 ms, turbo factor=4) and T2-weighted (TR=4500 ms, TE=83ms, turbo factor=11) images were acquired from MS patients for lesion segmentation, using 2D turbo-spin-echo sequences with 1x1x3 mm^3 voxel size, along with a matching 2D turbo FLAIR (Fluid-Attenuated Inversion Recovery) sequence with TR=9000 ms, TE=88ms, Inversion Time (TI)=2407.5 ms.

Image processing and structural MRI analyses were performed at the McConnell Brain Imaging Center by trained staff who were blinded to clinical and behavioural data. All images were evaluated for adequate signal-to-noise ratio, freedom from significant motion or other artifact, and consistency of the sequence parameters.

2.2.5.2 Lesion segmentation. A preprocessing routine was run first on all images to correct for intensity non-uniformity (Sled, Zijdenbos, & Evans, 1998), to remove skull and scalp (Smith, 2002), and to linearly register the T1-weighted images to the PD- and T2-weighted image to provide voxel-wise anatomical alignment across the modalities (Collins, Neelin, Peters, & Evans, 1994). Second, the intensity range was normalized within each image, using a two-piece linear transformation as described in Nyul and Udupa (1999). Third, using an interactive, mouse-driven visualization software package (DISPLAY, McConnell Brain Imaging Centre, Montreal Neurological Institute), the T2-weighted lesion labels output by an initial automated segmentation procedure were superimposed on the T1-, T2-, and PD-weighted images, carefully reviewed and, if necessary, manually corrected. Given their different MRI intensity characteristics, infratentorial T2-weighted lesions were segmented manually. Hypointense regions on T1-weighted images (T1-weighted lesions) located within the T2-weighted lesions were automatically segmented by applying an intensity threshold of 85% relative to the mean intensity of surrounding normal-appearing WM. Supratentorial and infratentorial lesion volumes were combined as a measure of total brain lesion volume.

2.2.5.3. Brain and thalamus segmentation. Three standard preprocessing steps were applied to the native T1-weighted images to delineate the thalamus. These included: (1) removing noise by using the optimized non-local means filter (Coupe, Hellier, Prima, Kervrann, & Barillot, 2008); (2) reducing the impact of intensity inhomogeneity due to RF coil variations using a non-parametric estimation of the slow varying non-uniformity field (Sled et al., 1998), and (3) normalizing the brain volume intensities to the intensities of the target template [i.e., the ICBM152 population template (Fonov et al., 2011)] by doing regression based analyses on image intensity percentiles.

The following steps were then conducted on the preprocessed images: (1) a mixture of linear and non-linear transformation (Collins et al., 1994) of the raw T1-weighted image to ICBM152 population template space (Fonov et al., 2011), (2) brain extraction using a library of tissue priors that are available in the ICBM152 population template (Eskildsen et al., 2012), (3) warping of the thalamus onto the raw T1-weighted image using the inverse of the transformation generated in step (1). Thalamic volumes were normalized for head size by dividing by total intracranial volume.

Normalized whole-brain GM and WM volumes were estimated using SIENAX (Smith, 2001; Smith, 2002b). First, the brain and skull were extracted from the T1 image (Smith, 2002). The brain image was then affine-registered to Montreal Neurological Institute (MNI)152 space, using the skull image to determine the registration scaling (Jenkinson, 2001; Jenkinson, 2002). Subsequently, tissue-type segmentation with partial volume estimation was carried out (Zhang, 2001) in order to calculate total volume of brain tissue.

Absolute volumes were reported for whole-brain GM, WM, and thalamus in cubic centimeters (cm^3). Normalization was used to enhance comparability of brain volumes across individuals with different skull size (associated with sex, race, or age).

2.2.5.4 Functional MRI acquisition and processing. fMRI images were acquired using a T2-weighted echo planar imaging sequence (TE=30ms, flip angle=90º, matrix size=86x64, field of view=256 x 190.5mm, TR=2s). Thirty-four axial slices, parallel to the anterior-posterior commissural plane (thickness = 4mm), covering the whole brain, were acquired during each measurement. Two dummy volumes were included at the beginning of the sequence, prior to the onset of the stimulus, allowing for the T1 recovery to reach a steady state.

Acquired images were converted from the DICOM (Digital Imaging and Communications in Medicine) to NIfTI (Neuroimaging Informatics Technology Initiative) file format, which is commonly used by neuroimaging software, using the dcm2nii command. Skulls were removed using the Brain Extraction Tool with manual centering for each participant.

Preprocessing was conducted using the FEAT (fMRI Expert Analysis Tool) program from the FMRIB Software Library. Images were slice-time corrected, motion corrected using a rigid-body algorithm in MCFLIRT (Motion Correction FMRIB Linear Image Registration Tool; Jenkinson, 2003), and temporally smoothed with a high-pass (100s cut-off) filter. Spatial smoothing was done with an 8mm (Full Width at Half Maximum) 3-dimesional Gaussian kernel. Each participant's functional images were spatially registered to their skull-stripped T1-weighted structural image, using Boundary-Based Registration (Greve & Fischl, 2009), which has demonstrated robustness to a range of pathologies. Subsequently, images were registered nonlinearly to standard MNI space (1mm), using a 10 mm warp resolution.

Correct trials on each of the task conditions (FW and AL) were modeled in FILM (FMRIB's Improved Linear Model) using a double-gamma function with temporal derivatives. In addition, six motion correction parameters, error trials, finger taps, and presentation of the set and probes were treated as covariates of no interest within the first level analysis. FILM prewhitening was applied to control for autocorrelation and temporal filtering was applied for low frequencies.

Voxel-wise parameter estimates were obtained for each participant, reflecting the fit of the model for task-related activation (ie. collapsed across executive demand) and a contrast of the executive demand conditions. The parameter estimate maps and variance maps for each participant were then forwarded into a whole-brain second level analysis, whereby inter-participant variability was treated as a random variable. Mixed effects analyses were performed using FLAME (FMRIB's Local Analysis of Mixed Effects; Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004). The contrast of executive demand conditions was collapsed across all participants to locate regions of the brain that demonstrated significant changes in Blood Oxygenation Level Dependent (BOLD) signal across the FW and AL conditions. Task-related activation (ie. collapsing across executive demand conditions) was compared across MS and HC groups to locate regions demonstrating a significant main effect of group. A comparison of MS

and HC groups on the executive demand contrast was conducted to identify regions demonstrating a significant interaction of group and executive demand.

Statistical maps were thresholded using voxels with a $z > 4.1$ and a (corrected) cluster significance level of $p < 0.0001$. Regions surviving this thresholding were labelled using Talairach Daemon Labels in the Wake Forest University PickAtlas (Lancaster, Summerln, Rainey, & Freitas, 1997; Lancaster et al., 2000; Maldjian, Laurienti, Kraft, & Burdette, 2003). Unique regions were reported with their maximum z-score and were used as ROIs by drawing a 10-mm sphere around each of the peak voxels within each cluster. The average percent signal change from these regions was then extracted and examined in order to investigate the effects of physical activity, as well as structural and performance correlates of recruited regions.

2.3 Statistics. The Shapiro-Wilk and Levene's tests were used to detect violations of normality and homogeneity of variance within data sets. Descriptive statistics were performed for the clinical characteristics of our MS sample (ie. age at disease onset, disease duration, number of relapses, EDSS score, use of disease-modifying therapies, T1 and T2 total lesion volumes). Groups were compared on demographic variables (age, sex, years education, handedness, socioeconomic status), as well as on depressive symptom classification, fatigue score, and self-reported physical activity level using independent samples *t*-tests, Mann-Whitney *U* tests, or Chi-square tests, where appropriate.

Measures of cognitive functioning, normalized brain volume (whole brain, GM, WM, thalamus), and physical activity were compared across MS patients and HCs by way of an independent samples t-test or Mann-Whitney U test, as appropriate. Outliers, defined as scores that lie above or below 3 standard deviations from the mean, were trimmed using a Winsorizing procedure to 3 standard deviations above/below the normative mean, where norms were available.

Performance on the Alphaspan task was assessed in a 2 (group) x 2 (executive demand) mixed measures analysis of variance (ANOVA), to examine main effects of group and executive demand, as well as a group x executive demand interaction. Given violations of the assumption of normality, the ANOVAs were broken down into three equivalent analyses, with parametric and non-parametric variants, as appropriate.

Correlations were conducted between physical activity and the % signal change in areas differentially recruited by MS patients, for MS patients and HCs separately. Cognitive

functioning and brain volumes were correlated with physical activity metrics, to enhance our understanding of relationships between activity level and cerebral activation. Correlations were also conducted between metrics of brain pathology (T1 and T2 lesion load, normalized brain volumes) and measures of cognitive function, task performance, and activation in regions recruited by MS patients, to better understand the contributory role of brain pathology to cognitive outcomes and recruitment strategies.

A correlation matrix including each of our variables was conducted to identify confounding variables to control for in our analyses. A conservative alpha of 0.01 was used across analyses to account for the increased type I error associated with multiple comparisons and correlations. One-tailed tests were used for analyses of directional hypotheses.

3. Results

3.1 Sample Characteristics. Two of the 24 MS patients and three of the 27 HCs in the study sample met criteria for cognitive impairment. One of these remaining 22 MS patients and four of the 24 HCs exceeded the movement criteria on the MRI task. Twenty cognitively-preserved MS patients and 20 HCs, matched for age and sex, were thus included in the final analyses. This final pediatric-MS sample did not differ from the original group of recruited patients on any demographic or disease-related variables (Appendix B).

Demographic and disease-related characteristics of the sample are reported in Table 1. Analyses confirmed that the pediatric-MS and HC groups were appropriately matched for age and sex, and did not differ significantly on any of the measured demographics. It is noted, however, that differences in socioeconomic status (SES) were near-significant across groups, with HCs showing a somewhat higher distribution. SES was thus taken into consideration as a potential confound in the interpretation of the results.

Performance on the battery of neuropsychological tests are reported in Table 2. The MS and HC groups did not differ significantly on any of the cognitive tasks, however, MS patients did demonstrate a trend toward poorer motor coordination on the 9HPT, as well as lower IQ, as measured via the WASI. In a post-hoc assessment with one-tailed tests, IQ did not correlate with age at disease onset ($r = 0.10$, $p = 0.339$), but demonstrated a near-significant correlation with SES ($r = 0.32$, $p = 0.090$).

MS patients demonstrated smaller normalized thalamic volumes than HCs, however, whole brain volumes (GM, WM) did not differ between groups (Table 3). MS patients also

Table 1

Demographic, MRI and MS-related Characteristics of Sample

	MS n = 20	**HC n = 20**	**Cohen's d**	**p-value**
Mean (range) age at scan	18.7 (14-23)	18.5 (13-22)	0.04	0.862
Sex (F/M)	15/5	15/5		1.000[a]
Handedness[b] (Right/Left)	18/2	17/3		0.633[a]
Mean (SD) years education	12.90 (2.47)	12.95 (2.31)	0.02	0.948
Mean (SD) Socioeconomic status – BSMSS score	44.78 (14.41)	52.55 (10.54)	-0.61	0.059
Mean (SD) disease duration[c], months	60.80 (39.94)			
Mean (SD) age at MS onset[d], years	13.05 (2.76)			
Mean (SD) number of relapses	4.60 (3.14)			
Median (range) physical disability rating, EDSS	1.50 (1.00-4.00)			
Current use of disease-modifying therapies (Y/N)	15/5			
Depression Symptom Classification (n: Normal/Mild/Major) – CES-DC[e]	12/3/5	15/4/1		0.208[a]
Mean (SD) Fatigue – PedsQL Multidimensional Fatigue score	57.69 (18.52)	63.94 (12.30)	0.44	0.217
Mean (SD) or median (range) level of physical activity[f], metabolic equivalents/ week	27.00 (0-63.00)	22.50 (0-81.00)	-0.01	0.978[g]
Strenuous	55.57 (25.29)	53.80 (32.81)	-0.06	0.849
Overall				

Note. MS = multiple sclerosis; HC = healthy control; F = female; M = male; BSMSS = Barratt Simplified Measure of Social Status; EDSS = Expanded Disability Status Scale Score; CES-DC = Centre for Epidemiological Studies Depression Scale for Children; PedsQL= Pediatric Quality of Life Inventory Multidimensional Fatigue Scale

a- Chi-square test
b- Based on Dutch Handedness Questionnaire
c- Months since first attack
d- Age at first attack
e- Classification based on Zich et al (1990) and Ensel (1986); scores of 16-26 are considered indicative of mild depression; scores >26 are indicative of major depression
f- Based on Godin-Shephard Leisure Time Activity Questionnaire
g- Mann-Whitney U test

Table 2

Group Comparisons on the Neuropsychological Battery, with Reported Means (SD) or Medians (Range)

	MS n = 20	**HC n = 20**	**Cohen's d**	**p-value**
Neuropsychological composite	0.38 (0.86)	0.38 (0.99)	0.00	0.999
Cognitive efficiency composite	0.19 (0.64)	0.42 (0.62)	0.37	0.265
RAVLT – Total Immediate Recall	-0.03 (1.21)	-0.12 (1.17)	0.08	0.818
RAVLT – Delayed Recall	-0.08 (-2.26-1.07)	0.33 (-0.78-1.44)	0.49	0.131[a]
WASI Full Scale IQ	0.34 (0.65)	0.69 (0.50)	0.58	0.076
WJ-III Auditory Working Memory	0.19 (0.68)	0.30 (0.58)	0.17	0.562
TMT-A	0.66 (-3.00-1.35)	0.49 (-1.38-1.58)	-0.03	0.925 [a]
TMT-B	0.55 (-3.00-1.56)	0.14 (-1.21-1.61)	-0.16	0.609 [a]
Nine Hole Peg Test (Right Hand)	-0.94 (-3.00-0.52)	-0.49 (-2.16-0.64)	0.71	0.035[a]

Note. MS = multiple sclerosis; HC = healthy control; RAVLT = Rey Auditory Verbal Learning Test; WASI = Weschler Abbreviated Scales of Intelligence; WJ-III = Woodcock-Johnson III Test of Cognitive Abilities – 3rd Edition; TMT-A and TMT-B = Trail Making Tests Parts A and B

a- Mann-Whitney U test

Table 3

Group Comparison of Structural Metrics (cm^3), with Reported Means (SD) or Medians (Range)

	MS **n = 22**	**HC** **n = 22**	**Cohen's d**	**p-value[a]**
Normalized Grey Matter Volume	849.84 (36.95)	860.03 (46.76)	0.24	0.225
Normalized White Matter Volume	691.48 (39.01)	705.72 (36.21)	0.38	0.120
Normalized Thalamic Volume	16.02 (11.70-18.00)	17.50 (16.15-18.56)	1.60	**< 0.001[b]**
Total T2 Lesion volume	4.27 (0.005-103.47)			
Total T1 Lesion Volume	2.18 (0-74.07)			

Note. MS = multiple sclerosis; HC = healthy control

a- one-tailed test, MS < HC

b- Mann-Whitney U test

demonstrated grossly variable T1 and T2 lesion volumes, with the majority of patients showing lesion volumes in the range of 1-8cm^3, and a subset of patients showing notably larger lesion volumes.

Total T1 lesion volume correlated negatively with the neuropsychological composite score (Table 4). Near-significant negative correlations were also observed between T1 lesion volume and cognitive efficiency, immediate and delayed recall on the RAVLT, the Trail Making Test (A & B), coordination on the 9HPT, and response time on the Alphaspan task. Similar correlations were observed for T2 lesion volume. Normalized global and regional brain volumes (GM, WM, thalamus) did not demonstrate significant correlations with the cognitive metrics, however, a near-significant association was observed between thalamic volume and performance on the 9HPT.

3.2 Alphaspan performance. As shown in Table 5, the analysis of task accuracy demonstrated a significant main effect of task demand, with participants performing more poorly on the AL task. Groups did not differ in task accuracy, and no group x executive demand interactions were observed. Percentage accuracy for the MS and HC groups in the FW and AL conditions are depicted in Figure 3.

As shown in Table 6, the analysis of response time revealed a near-significant effect of executive demand, with an average of 0.18s longer response time for the AL condition as compared to the FW condition. MS patients also demonstrated a near-significant, 0.21s longer, response time on the task than HCs. Response times for the MS and HC groups for each of the Alphaspan conditions are depicted in Figure 4. In one-tailed post-hoc tests, response time for MS patients demonstrated a stronger correlation with the cognitive efficiency score (r = -0.55, p = 0.006) than with motor coordination, as measured by the 9HPT (r = -0.21, p = 0.187). It is noted that the size of the response time differences may be negligible in the context of the functional analysis of the 7s delay period. No significant interaction was found.

3.3 Functional MRI results. Results of the whole-brain analyses demonstrated a significant effect of executive demand, as shown in Table 7. No significant activation differences were observed across groups, or via the analysis of group x executive demand interactions in the corresponding whole-brain analyses.

As group effects were not observed via the whole-brain analysis, areas demonstrating a main effect of executive demand were flagged as ROIs for a post-hoc assessment of group

Table 4

Correlations of Structural Metrics with Cognitive Outcomes in MS Patients, r-value (p-value)

Total Lesion Volumes		**T1 LV[a]**	**T2 LV[a]**
Cognitive measures			
Neuropsychological composite		**-0.54 (0.007)**	-0.47 (0.018)
Cognitive efficiency		-0.41 (0.035)	-0.37 (0.053)
RAVLT – Total Immediate Recall		-0.41 (0.036)	-0.38 (0.050)
RAVLT – Delayed Recall		-0.35 (0.067)	-0.32 (0.082)
WASI Full Scale IQ		0.08 (0.370)	0.04 (0.439)
WJ-III Auditory Working Memory		-0.17 (0.244)	-0.13 (0.297)
TMT-A		-0.34 (0.074)	-0.33 (0.081)
TMT-B		-0.34 (0.073)	-0.33 (0.080)
Nine Hole Peg Test (Right Hand)		-0.47 (0.020)	-0.45 (0.023)
Alphaspan Task *(collapsing across ED)*			
Accuracy		-0.06 (0.403)	-0.09 (0.354)
Response time		0.46 (0.020)	0.48 (0.017)
Normalized Brain Volumes	**GM**	**WM**	**Thal[a]**
Cognitive measures			
Neuropsychological composite	0.08 (0.377)	0.07 (0.392)	0.21 (0.186)
Cognitive efficiency	-0.08 (0.367)	0.18 (0.229)	0.05 (0.423)
RAVLT – Total Immediate Recall	-0.12 (0.305)	0.23 (0.166)	0.00 (0.495)
RAVLT – Delayed Recall	-0.01 (0.482)[a]	0.27 (0.128)[a]	0.02 (0.461)
WASI Full Scale IQ	-0.47 (0.019)	0.01 (0.481)	-0.13 (0.296)
WJ-III Auditory Working Memory	-0.06 (0.410)	0.11 (0.317)	-0.12 (0.307)
TMT-A	0.21 (0.183)[a]	-0.16 (0.252)[a]	0.28 (0.117)
TMT-B	0.27 (0.127)[a]	0.03 (0.444)[a]	0.20 (0.198)
Nine Hole Peg Test (Right Hand)	0.20 (0.194)[a]	-0.04 (0.434)[a]	0.33 (0.080)
Alphaspan Task *(collapsing across ED)*			
Accuracy	-0.19 (0.215)	-0.02 (0.466)	-0.14 (0.276)
Response time	-0.01 (0.492)	-0.09 (0.351)	0.01 (0.482)

Note. LV = lesion volume; RAVLT = Rey Auditory Verbal Learning Test; WASI = Weschler Abbreviated Scales of Intelligence; WJ-III = Woodcock-Johnson III Test of Cognitive Abilities – 3rd Edition; TMT-A and TMT-B = Trail Making Tests Parts A and B; GM = grey matter; WM = white matter; Thal = thalamus

a- Spearman's correlations

Table 5

Results of 2x2 Mixed ANOVA for Percentage Accuracy on the Alphaspan Task

			Cohen's d	p-value
Group x Executive Demand			0.38	0.241
	MS	**HC**		
Between: Group	90.63 (64.58-100)	90.62 (72.92-97.92)	0.15	0.644
	FW	**AL**		
Executive Demand	93.75 (70.83-100)	89.59 (54.17-100)	1.85	< **0.001**

Note. MS = multiple sclerosis; HC = healthy control; FW = forward; AL = alphabetize

Each component of the interaction was conducted with separate Mann-Whitney U analyses.

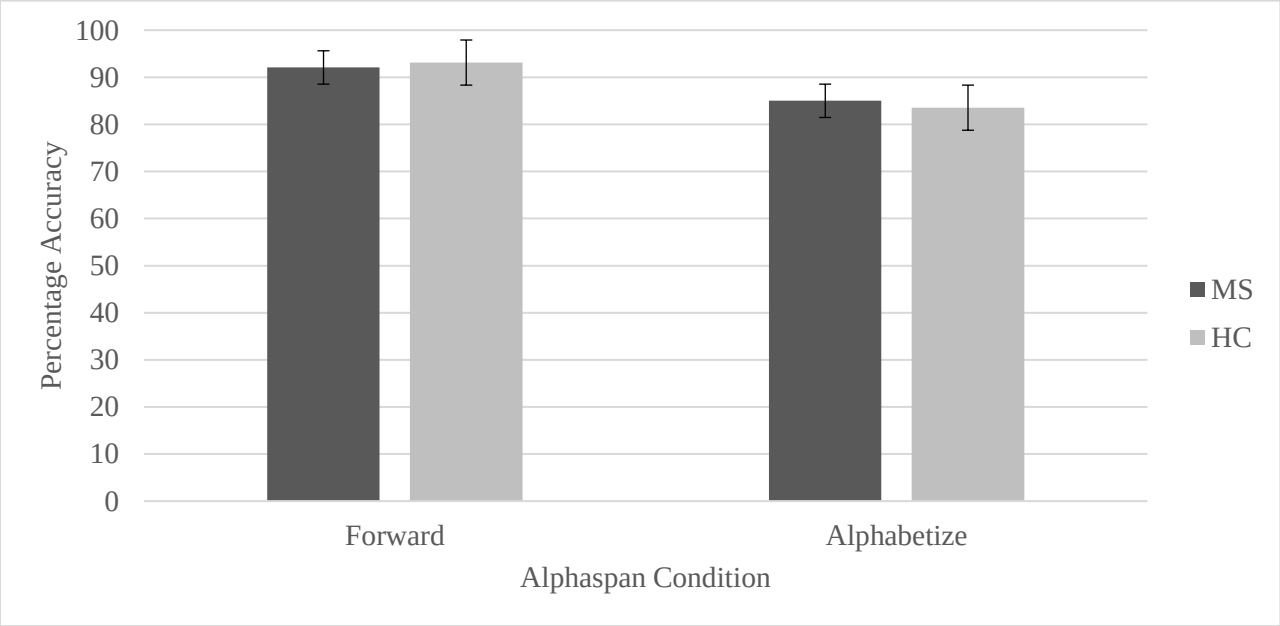

Figure 3. Percentage accuracy for MS and HC groups in the forward and alphabetize conditions of the Alphaspan task. Error bars reflect the standard error.

Table 6

Results of 2x2 Mixed ANOVA for Response Time (in seconds) on the Alphaspan Task

			Cohen's d	p-value
Group x Executive Demand			0.21	0.525
	MS	**HC**		
Between: Group	1.94 (0.28)	1.73 (0.33)	0.69	0.038
	FW	**AL**		
Within: Executive Demand	1.69 (1.29-2.56)	1.87 (1.02-3.13)	1.03	0.014[a]

Note. MS = multiple sclerosis; HC = healthy control' FW = forward; AL = alphabetize

Each component of the interaction was conducted separately, with parametric and non-parametric analyses, as appropriate.

a- Mann-Whitney U test

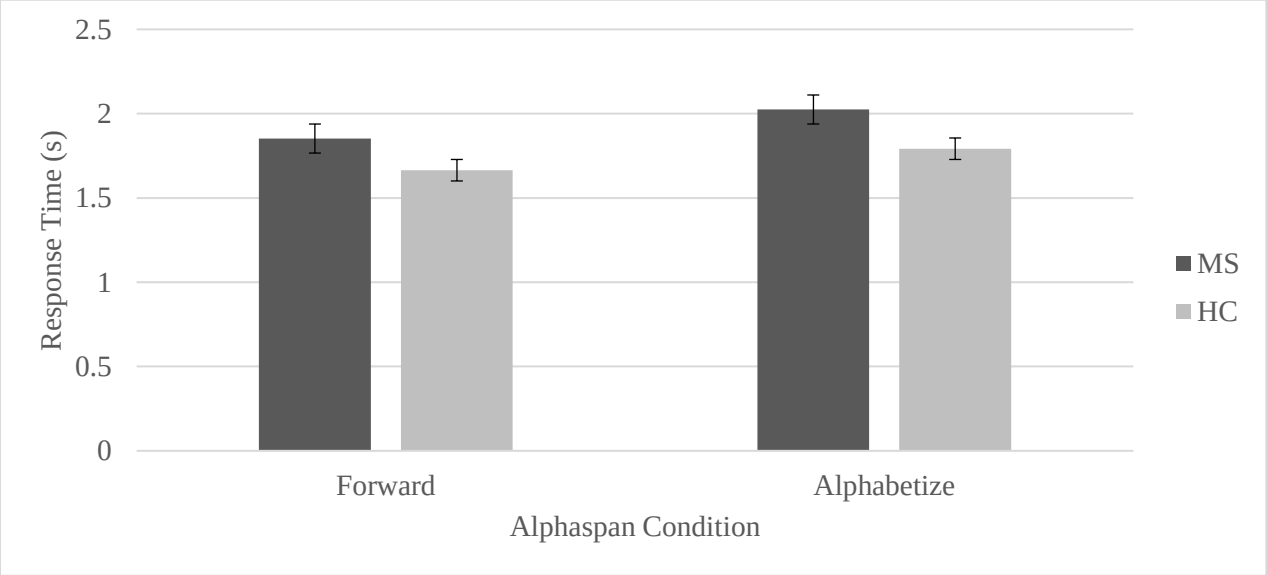

Figure 4. Response times for MS and HC groups in the forward and alphabetize conditions of the Alphaspan task. Error bars reflect the standard error.

Table 7

Areas Demonstrating Significant Difference in BOLD Signal When Contrasting Forward and Alphabetize Conditions

Region	BA	MNI coordinates (mm)			z-score	% signal change[a]
		X	Y	Z		
Frontal lobes						
L Superior	10	-6	57	2	6.50	-0.37
L Middle	9	-36	32	25	6.63	0.18
R Middle	6	33	4	53	6.25	0.25
L Inferior	44	-48	15	14	6.97	0.17
R Inferior	44	55	6	25	6.21	0.14
L Medial	8	-2	18	48	6.55	0.32
R Medial	32	2	50	-5	6.54	0.09
R Insula	13	32	21	2	6.50	0.16
L Precentral	6	-38	0	31	6.59	0.21
Parietal						
R Precuneus	7	10	-69	52	6.96	0.53
L Inferior	40	-37	-46	43	7.20	0.26
R Inferior	40	45	-41	45	7.27	0.33
R Postcentral	40	51	-36	50	7.26	0.31
Other						
L Parahippocampus	54	-23	13	-16	5.64	-0.18
R Parahippocampus	54	28	-23	-15	5.53	-0.11

Note. BA = Brodmann Area; MNI = Montreal Neurological Institute; L = left; R = right

a- Alphabetize > maintain

comparisons. Activation in the FW condition (vs. rest), activation in the AL condition (vs. rest), and upregulation/downregulation of activation across these conditions were compared in MS patients and HCs, as shown in Tables 8-10.

Activation in the right precuneus during the FW condition was significantly greater for MS patients, as compared with HCs. Near-significant differences ($p < 0.10$) across groups were found in both the FW and AL conditions, however, no interaction effects were observed. For both conditions, MS patients demonstrated greater recruitment than HCs in the right middle frontal gyrus, left medial frontal gyrus, left precentral gyrus, right precuneus, left inferior parietal gyrus, right inferior parietal gyrus, and right postcentral gyrus (Table 8-9).

These comparisons retained similar levels of significance when controlling for response time (Table 11), however activation in the left medial frontal gyrus during the AL condition no longer met the threshold for further exploratory analyses. Although other comparisons across groups did not reach statistical significance, there was a general trend towards MS patients showing enhanced activation/deactivation as compared to controls.

Recruitment of the right middle frontal gyrus was associated with poorer accuracy in the FW condition in MS patients, at a sub-threshold level ($r = -0.43$, $p = 0.059$). Near-significant associations were also observed for the right precuneus, right inferior parietal gyrus and right postcentral gyrus, between activation and poorer accuracy scores in the FW condition ($r = -0.44$, $p = 0.051$; $r = -0.41$, $p = 0.072$; $r = -0.39$, $p = 0.090$, respectively). For the AL condition, activation in the left precentral gyrus was near-significantly associated with greater accuracy ($r = 0.42$, $p = 0.066$). All other correlations did not approach significance, $p > 0.10$.

Smaller thalamic volumes were significantly associated with enhanced activation in the left inferior parietal gyrus during the FW condition, as well as during the AL condition at a near-significant level (Table 12). Greater T1 and T2 lesion volumes demonstrated near-significant correlations with enhanced recruitment of the left medial frontal gyrus, as well as with activation in the right middle frontal gyrus in the FW condition. T2 lesion volume also correlated positively with activation in the left inferior parietal gyrus in each of the task conditions, at a near-significant level. Although all remaining correlations between lesion volume and activation of regions differentially recruited by MS patients were in the direction anticipated, none approached significance.

Table 8

Region of Interest Analyses Comparing Activation in Forward condition (vs. rest) Across MS and HC groups

Region	Mean % signal change (SD) MS	HC	Cohen's d	p-value[a]
Frontal lobes				
L Superior	-0.18 (0.26)	-0.09 (0.20.)	-0.40	0.105
L Middle	0.11 (0.17)	0.07 (0.20)	0.23	0.235
R Middle	0.07 (0.13)	-0.01 (0.13)	0.64	0.025
L Inferior	0.13 (0.16)	-0.07 (0.14)	0.36	0.126
R Inferior	-0.02 (0.18)	-0.01 (0.14)	0.04	0.450
L Medial	0.26 (0.25)	0.09 (0.12.)	0.73	0.014
R Medial	-0.04 (0.19)	-0.03 (0.19)	0.08	0.403
R Insula	0.08 (0.16)	0.03(0.14)	0.36	0.420
L Precentral	0.21 (0.16)	0.13 (0.19)	0.45	0.080
Parietal				
R Precuneus	0.04 (0.27)	-0.17 (0.21)	0.84	**0.009**
L Inferior	0.26 (0.19)	0.15 (0.22)	0.56	0.042
R Inferior	0.13 (0.20)	0.02 (0.20)	0.53	0.052
R Postcentral	0.12 (0.17)	0.02 (0.18)	0.60	0.033
Other				
L Parahippocampus	0.07 (0.23)	0.07 (0.22)	0.02	0.477
R Parahippocampus	0.05 (0.18)	0.02 (0.22)	0.14	0.332

Note. MS = multiple sclerosis; HC = healthy control; L = left; R = right

a- one-tailed test, % signal change MS > HC

Table 9

Region of Interest Analyses Comparing Activation in Alphabetize Condition (vs. rest) Across MS and HC groups

Region	Mean % signal change (SD) MS	HC	Cohen's d	p-value[a]
Frontal lobes				
L Superior	-0.48 (0.35)	-0.54 (0.32)	0.20	0.276
L Middle	0.28 (0.28)	0.26 (0.27)	0.07	0.414
R Middle	0.33 (0.21)	0.22 (0.22)	0.50	0.060
L Inferior	0.29 (0.18)	0.26 (0.23)	0.32	0.292
R Inferior	0.09 (0.16)	0.17 (0.27)	-0.33	0.150
L Medial	0.62 (0.38)	0.47 (0.34)	0.43	0.092
R Medial	0.05 (0.27)	0.06 (0.23)	-0.06	0.419
R Insula	0.24 (0.21)	0.20 (0.19)	0.20	0.133
L Precentral	0.45 (0.22)	0.34 (0.28)	0.42	0.098
Parietal				
R Precuneus	0.56 (0.43)	0.29 (0.41)	0.63	0.026
L Inferior	0.54 (0.25)	0.42 (0.26)	0.44	0.084
R Inferior	0.46 (0.24)	0.35 (0.23)	0.49	0.064
R Postcentral	0.43 (0.21)	0.29 (0.21)	0.69	0.018
Other				
L Parahippocampus	-0.14 (0.32)	-0.09(0.30)	-0.15	0.310
R Parahippocampus	-0.08 (0.19)	-0.08 (0.23)	0.00	0.493

Note. MS = multiple sclerosis; HC = healthy control; L = left; R = right

a- one-tailed test, % signal change MS > HC

Table 10

Region of Interest Analyses in Contrast of Forward and Alphabetize Conditions in MS and HC groups

Region	Mean % signal change[a] (SD) MS	HC	Cohen's d	p-value
Frontal lobes				
L Superior	-0.30 (0.21)	-0.43 (0.37)	0.43	0.183
L Middle	0.17 (0.20)	0.20 (0.16)	-0.17	0.593
R Middle	0.26 (0.18)	0.24 (0.20)	0.14	0.657
L Inferior	0.16 (0.14)	0.17 (0.13)	-0.07	0.830
R Inferior	0.12 (0.13)	0.17 (0.17)	-0.36	0.269
L Medial	0.36 (0.30)	0.28 (0.33)	0.26	0.424
R Medial	0.10 (0.32)	0.09 (0.18)	0.01	0.972
R Insula	0.16 (0.14)	0.17 (0.12)	-0.06	0.539
L Precentral	0.24 (0.14)	0.18 (0.18)	0.33	0.300
Parietal				
R Precuneus	0.53 (0.37)	0.46 (0.35)	0.20	0.535
L Inferior	0.27 (0.16)	0.25 (0.17)	0.14	0.666
R Inferior	0.33 (0.17)	0.32 (0.22)	0.06	0.850
R Postcentral	0.31 (0.16)	0.27 (0.17)	0.26	0.411
Other				
L Parahippocampus	-0.21 (0.20)	-0.16 (0.16)	-0.27	0.390
R Parahippocampus	-0.12 (0.14)	-0.10 (0.07)	-0.20	0.530

Note. MS = multiple sclerosis; HC = healthy control; L = left; R = right

a- Alphabetize > Forward

Table 11

Examination of Areas Demonstrating Differential Recruitment Across Levels of Task Demand in MS Patients, Controlling for Response Time

Region	**Mean % signal change (SD)**		**p-value[a]**
	MS	**HC**	
R Middle Frontal *(FW vs rest)*	0.07 (0.13)	-0.02 (0.14)	0.041
R Middle Frontal *(AL vs rest)*	0.33 (0.21)	0.22 (0.22)	0.068
L Medial Frontal *(FW vs rest)*	0.26 (0.25)	0.09 (0.20)	0.016
L Medial Frontal *(AL vs rest)*	0.62 (0.38)	0.47 (0.34)	0.123
L Precentral *(FW vs rest)*	0.21 (0.16)	0.13 (0.19)	0.027
L Precentral *(AL vs rest)*	0.45 (0.22)	0.34 (0.28)	0.096
R Precuneus *(FW vs rest)*	0.04 (0.27)	-0.17 (0.21)	0.023
R Precuneus *(AL vs rest)*	0.56 (0.43)	0.29 (0.41)	0.026
L Inferior Parietal (*FW vs rest)*	0.26 (0.19)	0.15 (0.22)	0.030
L Inferior Parietal *(AL vs rest)*	0.54 (0.25)	0.42 (0.26)	0.067
R Inferior Parietal *(FW vs rest)*	0.13 (0.20)	0.02 (0.20)	0.049
R Inferior Parietal *(AL vs rest)*	0.46 (0.24)	0.35 (0.23)	0.032
R Postcentral *(FW vs rest)*	0.12 (0.17)	0.02 (0.18)	0.035
R Postcentral *(AL vs rest)*	0.43 (0.21)	0.29 (0.21)	0.011

Note. MS = multiple sclerosis; HC = healthy control; R = right; L = left; FW = forward; AL = alphabetize

a- one-tailed test, absolute % signal change MS > HC

Table 12

Correlations of Structural Metrics with Activation in Regions Differentially Recruited by MS Patients, r-value (p-value[a])

Total Lesion Volumes		**T1 LV[b]**	**T2 LV[b]**
R Middle Frontal *(FW vs rest)*		0.31 (0.091)	0.33 (0.079)
R Middle Frontal *(AL vs rest)*		0.34 (0.071)	0.35 (0.065)
L Medial Frontal *(FW vs rest)*		0.50 (0.012)	0.50 (0.031)
L Medial Frontal *(AL vs rest)*		0.45 (0.024)	0.46 (0.020)
L Precentral *(FW vs rest)*		0.26 (0.133)	0.30 (0.104)
L Precentral *(AL vs rest)*		0.12 (0.308)	0.14 (0.280)
R Precuneus *(FW vs rest)*		0.23 (0.162)	0.25 (0.140)
R Precuneus *(AL vs rest)*		0.19 (0.216)	0.23 (0.168)
L Inferior Parietal (*FW vs rest)*		0.23 (0.166)	0.32 (0.088)
L Inferior Parietal *(AL vs rest)*		0.28 (0.118)	0.35 (0.066)
R Inferior Parietal *(FW vs rest)*		0.36 (0.058)	0.35 (0.065)
R Inferior Parietal *(AL vs rest)*		0.33 (0.079)	0.31 (0.089)
R Postcentral *(FW vs rest)*		0.16 (0.246)	0.15 (0.263)
R Postcentral *(AL vs rest)*		0.22 (0.179)	0.18 (0.221)
Normalized Brain Volumes	**GM**	**WM**	**Thal[b]**
R Middle Frontal *(FW vs rest)*	-0.04 (0.428)	0.09 (0.349)	-0.03 (0.455)
R Middle Frontal *(AL vs rest)*	0.01 (0.483)	0.10 (0.332)	-0.18 (0.227)
L Medial Frontal *(FW vs rest)*	0.02 (0.470)	0.17 (0.233)	-0.11 (0.318)
L Precentral *(FW vs rest)*	-0.04 (0.430)	-0.00 (0.498)	0.03 (0.445)
L Precentral *(AL vs rest)*	0.07 (0.385)	0.36 (0.062)	0.12 (0.313)
R Precuneus *(FW vs rest)*	0.19 (0.212)	0.36 (0.124)	-0.10 (0.332)
R Precuneus *(AL vs rest)*	0.17 (0.242)	0.39 (0.090)	-0.13 (0.293)
L Inferior Parietal (*FW vs rest)*	-0.28 (0.117)	0.14 (0.286)	**-0.55 (0.006)**
L Inferior Parietal *(AL vs rest)*	0.05 (0.422)	0.33 (0.077)	-0.39 (0.043)
R Inferior Parietal *(FW vs rest)*	0.04 (0.441)	0.05 (0.420)	-0.00 (0.497)
R Inferior Parietal *(AL vs rest)*	0.07 (0.381)	0.191 (0.210)	-0.03 (0.455)
R Postcentral *(FW vs rest)*	0.02 (0.446)	-0.12 (0.301)	0.02 (0.467)
R Postcentral *(AL vs rest)*	-0.04 (0.429)	0.05 (0.418)	0.02 (0.475)

Note. LV = lesion volume; R = right; L = left; GM = grey matter; WM = white matter; Thal = thalamus; FW = forward; AL = rest

a- one-tailed test; greater activation associated with larger LV, and smaller GM, WM, Thal

b- Spearman's correlations

3.4 Physical activity correlation analyses. In exploring correlations between self-reported strenuous physical activity and BOLD signal in regions demonstrating differential activation in MS patients, a near-significant association was observed between higher physical activity and reduced activation in the right postcentral gyrus in the FW condition (Table 13). It is noted, however, that the direction of this association was opposite that anticipated in the one-tailed test. All other correlations were non-significant. Correlations between strenuous physical activity and activation in these regions did not approach significance in HCs.

Self-reported strenuous physical activity was not significantly correlated with any of the cognitive measures or with task performance in the MS patients or HCs. Strenuous physical activity level did, however, significantly correlate with larger whole brain WM volume in both MS patients and HCs. Strenuous PA also demonstrated a near-significant positive correlation with whole brain GM volume in MS patients, but not in HCs. Strenuous physical activity metrics did not correlate with lesion volume in MS patients. To enhance the interpretability of these findings, a post-hoc correlation was conducted between normalized brain volume (GM, WM) and physical disability; these relationships were non-significant, $p > 0.01$. Notably, in a separate one-tailed post-hoc assessment, higher levels of reported strenuous physical activity were associated with fewer MS relapses at a sub-threshold level, $r = -0.34$, $p = 0.070$.

3.4.1 Overall physical activity measure. The Godin measure of physical activity, measuring overall physical activity, did not significantly correlate with any of the cognitive measures or with task activation in MS patients or HCs. Notably, a near-significant positive correlation was observed between the Godin measure and the Cognitive Efficiency composite, $r = 0.39$, $p = 0.046$, in HCs. A positive correlation was also observed between the Godin measure and WM volume in HCs, $r = 0.59$, $p = 0.003$. Further, a near-significant positive correlation was observed between the Godin measure and GM volume ($r = 0.47$, $p = 0.018$) in MS patients.

Table 13

Strenuous Physical Activity Spearman Correlations

	MS group		HC	
	r	**p-value[a]**	**r**	**p-value[a]**
Cognitive measures				
Neuropsychological composite	0.23	0.167	-0.07	0.387
Cognitive efficiency	0.08	0.376	0.10	0.342
RAVLT – Total Immediate Recall	0.13	0.298	0.13	0.297
RAVLT – Delayed Recall	-0.12	-0.305	-0.12	0.311
WASI Full Scale IQ	-0.25	0.148	0.10	0.346
WJ-III Auditory Working Memory	0.26	0.130	0.11	0.329
TMT-A	-0.08	0.377	-0.05	0.412
TMT-B	-0.05	0.426	0.08	0.371
Nine Hole Peg Test (Right Hand)	0.09	0.359	-0.32	0.084
Alphaspan Task – *collapsed across executive demand*				
Reaction time	-0.07	0.391	0.14	0.274
Accuracy	-0.07	0.385	0.09	0.356
Structural metrics				
Normalized Grey Matter Volume	0.50	0.012	0.30	0.096
Normalized White Matter Volume	0.57	**0.005**	0.73	**<0.001**
Normalized Thalamic Volume	-0.02	0.472	0.16	0.253
Total T2 Lesion volume	0.14	0.283		
Total T1 Lesion Volume	0.16	0.245		
Differential activation in MS patients				
R Middle Frontal *(FW vs rest)*	0.14	0.274	0.12	0.303
R Middle Frontal *(AL vs rest)*	-0.02	0.473	0.19	0.214
L Medial Frontal *(FW vs rest)*	-0.12	0.315	0.13	0.297
L Precentral *(FW vs rest)*	-0.13	0.291	0.10	0.341
L Precentral *(AL vs rest)*	-0.06	0.401	0.01	0.487
R Precuneus *(FW vs rest)*	-0.03	0.444	-0.01	0.492
R Precuneus *(AL vs rest)*	0.15	0.265	0.16	0.244
L Inferior Parietal (*FW vs rest)*	-0.04	0.432	-0.10	0.340
L Inferior Parietal *(AL vs rest)*	0.14	0.281	-0.24	0.150
R Inferior Parietal *(FW vs rest)*	-0.26	0.134	0.09	0.351
R Inferior Parietal *(AL vs rest)*	0.03	0.443	0.18	0.230
R Postcentral *(FW vs rest)*	-0.35	0.064	-0.05	0.415
R Postcentral *(AL vs rest)*	-0.13	0.288	0.05	0.425

Note. MS = multiple sclerosis; HC = healthy control; RAVLT = Rey Auditory Verbal Learning Test; WASI = Weschler Abbreviated Scales of Intelligence; WJ-III = Woodcock-Johnson III Test of Cognitive Abilities – 3rd Edition; TMT-A and TMT-B = Trail Making Tests Parts A and B; R = right; L = left; FW = forward; AL = alphabetize

a- one-tailed test; higher level of strenuous PA associated with better performance on neuropsychological battery and Alphaspan task, larger brain volumes, smaller lesion volumes, and enhanced task activation

4. Discussion

In the current study, our objective was to assess whether patients with pediatric-onset MS who are cognitively intact demonstrate compensatory recruitment during executive control processing. We also set out to explore if one's level of functional recruitment is associated with their level of strenuous physical activity. Using exclusion criteria to establish groups of participants without cognitive impairment, we did not anticipate to observe differences between MS patients and HCs with respect to performance on the working memory task, despite the presence of brain pathology. These MS patients were, however, expected to demonstrate hyperactivation in task-related regions during a working memory task, and such activation was anticipated to correlate positively with their level of strenuous physical activity.

As anticipated, our sample of cognitively-preserved MS patients were able to complete a working memory task with increasing executive control demands at a level that was comparable to HCs. These patients did, however, demonstrate greater activation than controls on several regions associated with the working memory network. Contrary to our initial hypothesis, this pattern of recruitment was not positively correlated with one's level of engagement in strenuous physical activity. One near-significant negative correlation between reported strenuous activity level and activation in the right postcentral gyrus during the FW condition was noted.

4.1 Sample characteristics. Our final sample of cognitively-preserved pediatric-onset MS patients was comparable to pediatric-onset MS patient groups in the literature with respect to sex ratio, relapse rate, level of physical disability, and disease duration (Amato et al., 2008; MacAllister et al., 2007; Till et al., 2012). Our patient group was somewhat older at testing, as well as at disease onset, and as a consequence of our exclusion criteria, less varied with respect to their cognitive profiles than typical pediatric MS samples. This older age distribution reflects our intention to conduct neuroimaging on participants with more mature working memory networks, thus allowing for greater comparability between participants. The lack of significant differences between the original group of MS patients recruited for the study and the final group selected for further analysis suggests that application of exclusion criteria did not grossly change the representativeness of the sample with respect to disease-related and demographic characteristics.

Contrary to other studies (Amato et al., 2010; Grover et al., 2015a; Parrish, Weinstock-Guttman, Smerbeck, Benedict, & Yeh, 2013), our sample of MS patients did not demonstrate

significant differences from controls with respect to mood, fatigue, and level of physical activity. Given that our sample of MS patients was more cognitively intact than typical pediatric-MS samples, it is possible that these observations reflect a role of cognitive impairment on quality of life and engagement in health behaviours (Benito-Leon, Morales, & Riviera-Navarro, 2002; Hoogs, Kaur, Smerbeck, Weinstock-Guttman, & Benedict, 2011). Conversely, greater engagement in physical activity may have a beneficial impact on these symptoms (Pilutti, Greenlee, Motl, Nickrent, & Petruzzello, 2013; Ensari, Motl, & Pilutti, 2014).

4.1.1 Cognitive outcomes. The lack of cognitive differences between our MS group and HCs confirms that this group of patients not only lacks cognitive impairment, but is also of comparable cognitive performance to a group of age and sex matched HCs. Notably, only two MS patients were excluded when applying the criteria for cognitive impairment. This number was lower than what was anticipated based on the literature, perhaps reflecting interest to participate in those who are able to complete the fMRI tasks, as well as a capacity and willingness to travel to a new institution for the study. The older age at onset may also contribute to the lower incidence of cognitive impairment in our sample, as corresponding correlations have been reported in the literature (Amato et al., 2014; Banwell & Anderson, 2005; Hosseini, Flora, Banwell, & Till, 2014; Till et al., 2011). The number of controls that were excluded was somewhat higher than anticipated (Ingraham & Aiken, 1996), perhaps reflecting reduced motivation to participate and engage fully in the tasks by controls who may be engaging in the study through course requirement.

It is noted that IQ differences between groups were near-significant. Although lower IQ (and particularly verbal IQ) has been observed in pediatric-onset MS, these deficits have more typically been seen with patients demonstrating an earlier onset (Amato et al., 2008; Till et al., 2011). As IQ was not correlated with age at onset, but did correlate with SES, these results may reflect pre-existing differences as opposed to IQ differences resulting from MS pathology. This hypothesis is further supported via the lack of correlation between IQ and lesion volume in MS patients.

A near-significant difference on the 9HPT between MS patients and HCs suggests that motor coordination problems may be more sensitive to MS pathology than cognitive outcomes. This maps onto adult literature showing that fine motor dysfunction is one of the early symptoms

of MS (Benedict et al., 2011). Similar results have been found in pediatric-onset MS, however, few studies have focused on this deficit (Julian et al., 2013; Squillace, Ray, & Milazzo, 2014).

4.1.2 Structural MRI metrics. Lesion volumes in our sample of MS patients were comparable to those reported in similar studies (Till et al., 2011; 2012). It is noted that there was considerable variability in the volume of lesions observed across participants; however, this observation has been quite consistent across studies.

MS patients demonstrated smaller thalamic volumes than HCs. Similar findings have been reported by Kerbrat et al (2012), Mesaros et al (2008) and Till et al (2011), suggesting that the thalamus is particularly sensitive to MS pathology. This vulnerability may be due to its proximity to the ventricles (Houtchens et al., 2007), or reflect Wallerian degeneration from widespread WM pathology given the thalamus' involvement in cross-cortical connections (Mesaros et al., 2008).

Although MS patients, on average, demonstrated smaller GM and WM volumes than HCs, these volumes were not significantly smaller than HCs. It is possible that the relative sparing of whole brain volumes reflects a lack of significant disease progression or more effective repair mechanisms in this sample, as lower volumes are anticipated to reflect secondary disease mechanisms, such as Wallerian degeneration or lack of age-expected growth.

4.1.3 Relationships between structural MRI metrics and cognitive outcome. T1 lesion volume correlated negatively with the Neuropsychological Composite score. Moreover, a trend toward poorer cognitive scores in individuals with larger T1 and T2 lesion volumes was observed across most cognitive and motor measures. Similar correlations were observed with measures of response time on the Alphaspan task, however, lesion volume did not correlate with accuracy scores. These findings suggest that those with greater disease burden demonstrate poorer functional outcome, even in patients demonstrating sub-clinical cognitive deficits. It is noted, however, that only up to 29% of the variance in functional outcome was accounted for by lesion burden.

Contrary to relationships observed with lesion volumes, normalized brain volumes were generally not predictive of cognitive outcomes in this sample. These correlations may lack significance given the lack of volume loss (or more typical age-expected growth) observed in this population. It is noted that thalamic volume correlated at a near-significant level with

performance on the 9HPT. This is not surprising, given the role of the thalamus in coordinating movements and its sensitivity to MS pathology (Tekin & Cummings, 2002).

4.2 Alphaspan performance. As expected, greater executive demand on the Alphaspan task was associated with slower response times and reduced accuracy, reflecting the greater challenge posed by the condition requiring manipulation of the stimuli relative to the simpler demand of maintenance. Given the relatively normal cognitive performance of our sample of MS patients, accuracy on this task did not differ across the MS and HC groups. It is noted, however, that MS patients may be able to perform executive function tasks comparably to controls when sufficient time is provided (Leavitt et al., 2014).

A somewhat slower response time was observed in MS patients, which was associated with cognitive efficiency, as opposed to fine motor coordination. This suggests that the slowed response time was more likely attributable to slowed processing speed, as opposed to difficulties pressing the button. This apparent sensitivity of processing speed to MS pathology, in a relatively cognitively-preserved sample, maps onto the literature advocating for use of the SDMT as a screener for cognitive dysfunction (Chavret, Beekman, Amadiume, Belman, & Krupp, 2014). Notably, these response time differences did not appear to disrupt the comparison of hemodynamic response functions across MS patients and HCs for the Alphaspan task. The 0.23s difference in response time is small in the context of the 7 second delay period, over which BOLD activation was averaged. Further, activation differences across these groups that neared significance retained comparable p-values in analyses that included response time as a covariate.

4.3 Functional MRI results. Whole-brain analyses, collapsing across all participants, identified areas demonstrating BOLD signal changes across the low and high executive demand conditions. These areas mapped onto those observed in working memory research (left superior frontal gyrus (du Boisgueheneuc et al., 2006; Tomasi, Ernst, Caparelli, & Chang, 2006), middle frontal gyri (Curtis & D'Esposito, 2003; Crone et al., 2006; Wager & Smith, 2003), medial frontal gyri (Courtney, Petit, Maisog, Ungerleider, & Haxby, 1998; Wager & Smith, 2003), inferior frontal gyri (Crone et al., 2006; Smith & Jonides, 1999), right insula (Menon & Uddin, 2010), left precentral gyrus (Curtis & D'Esposito, 2003), right precuneus (Cavanna & Trimble, 2006; Wager & Smith, 2003), inferior parietal gyri (Baldo & Dronkers, 2006; Deschamps, Baum, & Gracco, 2013; Ravizza, Delgado, Chein, Becker, & Fiez, 2004), parahippocampal gyri (Luck et al., 2010; Tomasi et al., 2006). Activation in the right postcentral gyrus has not been

observed consistently in neuroimaging studies of working memory, however, it is noted that the coordinates for this region overlapped with the supramarginal gyrus (BA 40), which has been associated with phonological processing in verbal working memory tasks (Baldo & Dronkers, 2006; Deschamps et al., 2013; Ravizza et al., 2004). The observed deactivation of the left superior frontal gyrus and parahippocampal gyri are believed to reflect a transition away from the default mode network activation during rest (Uddin, Kelly, Biswal, Castellanos, & Milham, 2009).

In the corresponding whole-brain analyses of group differences and group by executive demand interactions, no significant activations were observed. This may reflect a lack of power given stringent corrections for type I error in the whole-brain analyses. Upon probing ROIs associated with task activation in the whole-brain analysis of a main effect of executive demand, several regions were found to show enhanced activation in MS patients. However, no significant interaction was found, suggesting that the upregulation of neural resources with increasing executive control demands was not significantly different between MS patients and HCs.

The regions that appeared to be differentially recruited by MS patients included the right middle frontal gyrus, left medial frontal gyrus, left precentral gyrus, right precuneus, bilateral inferior parietal gyri and right postcentral gyrus. Activation in these regions were generally associated with reduced accuracy on the task on the FW condition, suggesting that those who have greater difficulty on the task demonstrate enhanced recruitment in these regions. Similar inverse relationships between resting-state functional connectivity and cognitive performance have been observed in another study conducted by our group using a subset of the current sample (Akbar et al., 2016). Conversely, Akbar et al (2015) demonstrated positive associations between activation during an fMRI version of the SDMT and task performance.

Reuter-Lorenz and Cappell (2008) note that differential activation associated with poorer performance is typically attributed to maladaptive processes, such as multiple or inefficient strategies, and/or disinhibition related to reduced interhemispheric communication. This interpretation is supported by the corpus callosum pathology typically observed in pediatric-onset MS patients (Till et al., 2011; Vishwas, Chitnis, Pienaar, Healy, & Grant, 2009). Notably, as our group of MS patients demonstrated comparable levels of task accuracy to HCs, and the regions recruited were in areas anticipated for the task, these activations may alternatively reflect imperfect compensatory mechanisms. In particular, recruitment of prefrontal regions may be

explained as an increased need for cognitive control to accommodate processing deficiencies or disinhibition elsewhere in the brain (Hillary, 2008; Reuter-Lorenz & Cappell, 2008). Reflecting on Akbar et al's (2015) findings in conjunction with the current study, increased activation may occur in cognitively-preserved pediatric-MS patients and be effective in enhancing performance for well-practiced tasks, such as the SDMT, but be limited in facilitating performance on tasks requiring executive control. Notably, the only area demonstrating a positive relationship with task accuracy was the left precentral gyrus, which likely plays a role in regulating the physical response to the task.

Enhanced activation in the right middle frontal, left medial frontal, left precentral, and/or parietal regions during working memory tasks has been described in adults with MS (Amann et al., 2011; Hillary et al., 2003), cognitively-preserved adults with MS (Mainero et al., 2004), as well as during the Alphaspan in adults with TBI (Turner et al., 2009). Recruitment in the right middle frontal gyrus and left precentral gyrus in MS patients was in the premotor cortex, which is believed to play a role in the maintenance of specific types of information, such as prospective motor intentions (Curtis & D'Esposito, 2003); this activation could reflect preparation for the finger tap in the right hand. Activation in this region has also been observed to be sensitive to executive demand (Wager & Smith, 2003).

The left medial frontal gyrus in this case represents the frontal eye fields, which facilitate spatial rehearsal during working memory tasks (Courtney et al., 1998). The parietal regions differentially recruited in MS patients represent the precuneus, which plays a role in visuospatial imagery (Cavanna & Trimble, 2006), and the supramarginal gyrus, which has been reported to play a role in executive processes or phonological processes depending on the sub-region (Baldo & Dronkers, 2006; Deschamps et al., 2013; Ravizza et al., 2004). Enhanced activation in these regions are believed to reflect greater resources required for executive control processing or rehearsal in the Alphaspan task.

4.3.1 Relationships between structural MRI metrics and functional recruitment.

Recruitment of the right middle frontal gyrus, left medial frontal gyrus, and left inferior parietal regions demonstrated near-significant correlations with total lesion volume. These results suggest that disease burden is predictive of the extent of recruitment required by these youth with MS. Greater thalamic damage was associated with increased recruitment of the left inferior parietal gyrus. As thalamic volume corresponds closely to lesion volume, this relationship may

similarly reflect the extent of recruitment required by individuals that have more pathology. Whether thalamic volume bears a specific relationship to activation in the inferior parietal gyrus is unclear; however, it is noted that connections corresponding to oculomotor fronto-subcortical networks do exist between these regions (Tekin & Cummings, 2002).

Although greater lesion volume was consistently associated with cognitive outcome metrics, no correlation was observed with working memory, suggesting that this function may be less sensitive to disease burden. Taking into consideration the observation of enhanced recruitment during the Alphaspan task, the lack of association between lesion volume and performance on working memory tasks may reflect a greater capacity for patients to compensate for complex functions that utilize a distributed network. As lesion volumes correlated with activation in recruited areas, it is possible that disease burden is more predictive of greater cognitive effort in working memory tasks than actual performance in patients who are cognitively preserved. The apparent sensitivity of working memory to MS pathology in other studies in which one-third of the sample was identified as having cognitive impairment (Till et al., 2011) may reflect more advanced pathology disrupting widespread networks, or WM difficulties attributable to slowed processing speed, learning and memory problems, or executive difficulties related to sequencing or shifting.

Our findings highlight that although structural MRI measures of disease burden (and particularly lesion volume) do demonstrate relationships with cognitive outcomes, they only modestly explain the variability in such outcomes. Observed relationships between disease burden and BOLD signal during a working memory task enhance our understanding of the role of MS pathology on inefficient neural processes and/or the development of compensatory mechanisms in cognitively-preserved pediatric-MS patients. Greater insight into the underlying mechanisms allowing patients to retain cognitive function may allow us to better understand the imperfect relationship between MS pathology and cognitive outcomes. We now turn to our exploration of physical activity as a predictor of functional outcome.

4.4 Physical activity correlations. Contrary to our hypothesis, physical activity did not generally demonstrate strong correlations with activation in regions recruited by MS patients; however, increased strenuous activity was moderately associated with reduced activation in the right postcentral gyrus during the FW condition. This pattern is contrary to our original hypothesis that physical activity would be associated with enhanced activation in recruited

regions, but may instead reflect that those engaging in higher levels of activity may not need to recruit a region as much for adequate task performance.

Given the lack of correlation between physical activity and BOLD signal during the task, it is unclear whether physical activity plays no mediating or moderating role in these neural processes, or if there are several mechanisms at play which mask each other. For instance, physical activity may both enhance the efficiency of neural processes (Chaddock et al., 2012; Chaddock-Heyman et al., 2013), leading to *reduced* activation required for a task, and contribute to neuroplastic processes that lead to *greater* recruitment during a task (Prakash et al., 2007).

Measures of physical activity did not correlate with cognitive outcomes in MS patients or HCs. No other studies have explored the relationship between physical activity and cognitive function in pediatric-onset MS patients, however, it is noted that our findings may be limited in applicability given the lack of variability in function associated with the cognitive preservation of our sample. Cognitive preservation may not fully explain the lack of correlation, however, as corresponding relationships have been observed in healthy populations without impairment (Hotting & Roder, 2013). Our lack of sensitivity to these relationships may thus also be attributable to our measure of physical activity. We used a questionnaire that does not distinguish between activities that require cognitive involvement or include therapeutic components, which are factors proposed to mediate the relationship between physical activity and cognitive function (Diamond & Ling, 2015).

A significant relationship was observed between strenuous physical activity and normalized WM volume in both MS patients and HCs, and a near-significant relationship was observed with normalized GM volume in MS patients. It is noted that the directionality of the relationship between physical activity and brain volume cannot be concretely established. Individuals with larger brain volumes did not, however, demonstrate less severe physical symptoms (as measured by the EDSS), suggesting that it is unlikely that higher brain volume predicts engagement in physical activity level via lower disease severity.

Although, in the context of this study, the role of physical activity in predicting brain volumes is speculative, previous studies have observed enhanced synaptogenesis and angiogenesis in rodents (Berggren et al., 2014; Vaynman et al., 2005), as well as reduced disease progression in MS patients (Motl et al., 2012). Given the observed negative relationship between strenuous physical activity and relapse rate, it is possible that increased strenuous physical

activity is protective of volume losses via reduced accrual of relapses and progressive neurodegeneration. Similar relationships have been reported by Grover et al (2015b). It is noted, however, that a relationship was not observed between this measure of physical activity and lesion volume nor thalamic volume, suggesting that although strenuous physical activity may reduce disease activity, it was not associated with reduced disease burden in our sample.

Comparing the correlations observed in MS patients and HCs, it appears that physical activity more typically contributes to larger WM volumes. This relationship is particularly strong in HCs, suggesting that MS pathology may counteract the positive relationship between physical activity and WM volume. Conversely, the relationship between physical activity and GM volume was stronger in MS patients than in HCs, suggesting that rather than physical activity leading to growth of GM, it may rather protect against GM loss.

This hypothesized protective role of physical activity is supported by the observation of a negative association between reported strenuous physical activity and activation in the right postcentral gyrus during the FW condition, which is low in HCs. If physical activity protects against MS-related brain pathology, there may be fewer maladaptive activation patterns (ex. disinhibition), as well as less of a need to engage compensatory strategies. Such mechanisms may also explain why we do not see a relationship between physical activity and cognitive outcomes in our cognitively preserved sample.

Similar patterns were observed for the strenuous and overall (ie. Godin) measures of physical activity, however, these correlations were less likely to approach significance when conducted with measures of overall physical activity. The strenuous activity measure of the Godin specifically asks participants to comment on their engagement in activities that make them sweat, thus tapping into aerobic activity level. These findings thus align with the literature suggesting that aerobic activity is particularly protective of brain structure and function (Colcombe & Kramer, 2003; Prakash et al., 2010).

4.5 Limitations and future directions. The current study is limited by the lack of a cognitively impaired comparison group. While our homogeneous patient group provided us with the opportunity to investigate task-based activation patterns, the results are not generalizable to the pediatric MS population as a whole. Moreover, a longitudinal design is needed to attribute cognitive preservation to enhanced activation in task-related regions. The use of global brain volumetrics also limit our capacity to understand how anatomically-specific atrophy or lack of

growth may relate to cognitive function or the necessity to differentially recruit brain regions during a working memory task. Furthermore, with the use of a physical activity questionnaire, we cannot rule out the possibility of biases in self-report.

Future studies should examine how activation patterns compare in cognitively impaired and preserved MS patients. It will also be important to investigate how activation patterns evolve as the disease progresses; for instance, it is uncertain whether a ceiling effect may ultimately occur, reflecting exhaustion of compensatory mechanisms. Given the stronger relationships observed between disease burden and other outcome metrics such as fine motor coordination, studies investigating such metrics may be better able to observe what activation patterns occur when recruitment mechanisms are exhausted or unavailable. Examination of activation patterns in different cognitive paradigms will also be important to examine whether individuals are differentially able to engage in recruitment for cognitively simpler vs. complex tasks (or tasks that require smaller vs. widespread networks).

Given the relative functional-specificity of brain regions, and variability in lesion location across patients, it is important to consider that recruitment strategies likely differ at the individual level. Exploration of such strategies would thus make for an interesting investigation, dissimilar to many initiatives in neuroimaging. In addition, as there is limited clarity in the interpretation of enhanced activation as either adaptive or maladaptive, it would be beneficial to measure participants' subjective experience through the task. This may provide insight on whether participants are aware of utilizing alternative strategies or exerting greater effort.

The role of physical activity on cognitive function in patients with pediatric-onset MS can be better explored with more direct and objective measures of aerobic physical activity or fitness, such as by accelerometry or VO_2max testing. Understanding of these relationships can be optimized in randomized control trial studies of an aerobic activity intervention. In considering a potential limited impact of physical activity on cognitive function in pediatric-onset MS patients, other potential predictors of cognitive reserve should be explored, including premorbid IQ and level of engagement in cognitive tasks, among others.

4.6 Conclusions. In summary, pediatric-onset MS patients are able to retain relatively intact cognitive function, despite MS pathology. Although lesion volume is predictive of cognitive performance in these individuals, these relationships are weak to moderate at best

(accounting for less than 29% of the variance), suggesting that other mechanisms are at play which allow individuals to adapt around such pathology.

We found that cognitively preserved pediatric-onset MS patients demonstrate enhanced activation of task-related regions during a working memory task. Despite comparable performance to HCs, activation in recruited regions was enhanced for patients demonstrating greater difficulty on the task, suggesting that such activation may reflect subclinical inefficiencies in task processing and/or compensatory recruitment.

Greater engagement in strenuous physical activity was associated with larger GM and WM volumes in MS patients, as well as greater efficiency of activation in the right postcentral gyrus, which was recruited in MS patients during the low executive demand condition of the working memory task. Given the negative relationship between physical activity and relapse rate, it is suggested that physical activity may be protective of brain structure and function, as opposed to enhancing.

These results suggest that, although pediatric-onset MS patients may not demonstrate deteriorations in performance early in the disease course, they may experience greater disorganization in cognitive strategies or utilize greater neural resources to complete a task. This is important to consider when setting expectations and time limits in school and other contexts, as greater demand on neural networks could contribute to grade retention in this population (Mikaeloff et al., 2010).

Although relationships between physical activity and cognitive function remain unclear, results of the current study echo previous findings suggesting potential benefits of strenuous activity on brain volume, and potentially disease progression. Recommendations for youth with MS to engage in greater aerobic activity are important to consider given the lower levels of physical activity reported in MS populations (Grover et al., 2015a; Grover et al., 2015b; Motl et al., 2015).

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Appendix A

MRI safety form

York University Neuroimaging Laboratory

Magnetic Resonance (MR) Safety Screening Form

Name _____ **Weight** _____

Last First MI **Height** _____

Date of Birth ____/____/____ ❑ Male ❑ Female

Month Day Year

Do you have: **Cardiac pacemaker or implantable cardioverter defibrillator (ICD)** ❑ **Yes** ❑ **No**

Aneurysm clip ❑ **Yes** ❑ **No**

Are you: Claustrophobic ❑ Yes ❑ No

Are you currently taking any medications? ❑ Yes ❑ No

List: _____

Have you ever had an injury to the eye involving a metallic object or fragment? ❑ Yes ❑ No

Have you ever worked in a metal shop? ❑ Yes ❑ No

Possibility of pregnancy? ❑ Yes ❑ No ❑ Not applicable

Brain/Head Surgery ❑ Yes ❑ No

List type/date

Heart/Chest Surgery ❑ Yes ❑ No

List type/date *Retained pacer wires* ❑ Yes ❑ No

Ear Surgery ❑ Yes ❑ No

List type/date

Eye Surgery ❑ Yes ❑ No

List type/date

Artificial Implants/Mechanical Devices .

List type/date ❑ Yes ❑ No

Other Surgery.

List type/date ❑ Yes ❑ No

Pierced body parts (earrings, etc.) ❑ Yes ❑ No

Hearing aid or cochlear implant ❑ Yes ❑ No

Permanent retainer or braces ❑ Yes ❑ No

Dentures or partials ❑ Yes ❑ No

History of bullets, shrapnel or BBs ❑ Yes ❑ No

History of seizures ❑ Yes ❑ No

Hair piece, wig or hair extensions ❑ Yes ❑ No

Medication or transdermal patch ❑ Yes ❑ No

Tattoo or permanent makeup ❑ Yes ❑ No

Stent, filter ❑ Yes ❑ No

WARNING: Certain implants, devices, or objects may be hazardous to you and/or may interfere with the MR procedure (i.e., MRI, MR angiography, functional MRI, MR spectroscopy). **Do not enter** the MR system room or MR environment if you have any questions or concerns regarding an implant, device, or object. Consult the MRI Technologist or Researcher BEFORE entering the MR system room. **The MR system magnet is ALWAYS on.**

I attest that the above information is correct to the best of my knowledge. I have read and understood the contents of this form and had the opportunity to ask questions regarding the information on this form and regarding the MRI procedure that I am about to undergo.

Signature of person completing form: _____ **Date** ___/___/___

M D Y

Form completed by: ❑ MRI participant ❑ Other (specify)_____

Reviewed by: _____ **PI of study** _____

Appendix B

Assessment of demographic variables in recruited MS participants vs. those retained in final analyses (ie. after application of exclusion criteria)

	Recruited n = 24	**Final n = 20**	**p-value**
Mean (range) age at scan	18.7 (13-24)	18.7 (14-23)	0.975
Sex (F/M)	17/7	15/5	1.000[a]
Handedness (Right/Left)[b]	21/3	18/2	0.904[a]
Mean (SD) years education	12.67 (2.57)	12.90 (2.47)	0.761
Mean (SD) Socioeconomic status – BSMSS score	44.38 (13.95)	44.78 (14.41)	0.926
Mean (SD) disease duration, months[c]	59.13 (37.98)	60.80 (39.94)	0.888
Mean (SD) age at MS onset, years[d]	13.21 (2.69)	13.05 (2.76)	0.849
Mean (SD) number of relapses	4.08 (3.09)	4.60 (3.14)	0.587
Median (range) physical disability rating, EDSS	1.50 (1.00-4.00)	1.50 (1.00-4.00)	0.863[e]
Current use of disease-modifying therapies (Y/N)	18/6	15/5	1.000[a]
Depression Symptom Classification[f] (n: Normal/Mild/Major) – CES-DC	16/3/5	12/3/5	0.901[a]
Mean (SD) Fatigue – PedsQL Multidimensional Fatigue score	60.46 (18.62)	57.69 (18.52)	0.625
Mean (SD) or median (range) level of physical activity, metabolic equivalents/ week[g]			
Strenuous	24.75 (0-63.00)	27.00 (0-63.00)	0.775[e]
Overall	53.23 (24.98)	55.57 (25.29)	0.759

Note. F = female; M = male; BSMSS = Barratt Simplified Measure of Social Status; EDSS = Expanded Disability Status Scale Score; CES-DC = Centre for Epidemiological Studies Depression Scale for Children; PedsQL= Pediatric Quality of Life Inventory Multidimensional Fatigue Scale

a- Chi-square test
b- Based on Dutch Handedness Questionnaire
c- Months since first attack
d- Age at first attack
e- Mann-Whitney U test
f- Classification based on Zich et al (1990) and Ensel (1986); scores of 16-26 are considered indicative of mild depression; scores >26 are indicative of major depression
g- Based on Godin-Shephard Leisure Time Activity Questionnaire