

FUNCTIONAL MRI ACTIVATION OF INHIBITORY CONTROL IN ADOLESCENTS AND
YOUNG ADULTS WITH MULTIPLE SCLEROSIS

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Abstract

Inhibitory control refers to the ability to selectively attend to stimuli over a period of time and to inhibit unwanted responses. This ability is rarely compromised in patients with multiple sclerosis (MS), despite frequent impairment in other executive functions, even at early stages of the disease. The role of functional reorganization in the preservation of cognitive abilities has been documented in adults with MS, but has received little attention in children and adolescents who have MS. The current study examined: (1) inhibitory control using a Go/No-go task (GNG) in patients and age-matched controls; (2) the relationship between GNG performance and measures of cerebral tissue damage and age at disease onset; and (3) patterns of neural activation associated with inhibitory control on the GNG task. Twenty pediatric-onset relapse remitting MS patients (13 females; age 19.36 ± 2.99) and 17 age- and sex-matched healthy controls (14 females; age = 19.26 ± 2.63) performed a simple GNG task while in a 3T MRI scanner. Participants pushed a response button when they viewed a green spaceship (Go stimulus), but not when they viewed a red spaceship (No-go stimulus). Go versus No-Go stimuli were presented at a ratio of 5:1 over 2 blocks. A brief neurocognitive screening assessment and questionnaires were also completed following the GNG task. Patients and controls did not differ with respect to IQ ($p = 0.77$), neuropsychological functioning on a battery of tests, nor on reaction time ($p = 0.13$) and accuracy ($p = 0.87$) on the GNG task. Age at evaluation, fatigue, depression symptoms, and fine motor dexterity on the 9 Hole Peg Test did not correlate with GNG performance parameters. Younger age at disease onset (controlling for disease duration) was marginally associated with lower accuracy on the GNG task ($r = 0.38$, $p = 0.054$), suggesting that a less mature brain may be less capable of using functional reorganization as an adaptive

mechanism to preserve inhibitory control. Regarding structural MRI correlates of GNG performance, T1-weighted lesion volume trended with lower accuracy on the GNG task ($r = -0.32, p < 0.10$). Using a whole brain approach, the control group demonstrated greater functional activation than patients when inhibiting a response in the following eight brain regions: cerebellum, brainstem, lateral occipital cortex, parahippocampal gyrus, precuneus, superior parietal lobe, precentral gyrus and superior frontal gyrus. These findings demonstrate that cognitively intact pediatric-onset MS patients recruit fewer brain regions than controls on a simple inhibitory control task. In particular, functional abnormalities of the posterior and anterior regions of the response inhibition network in the MS group were identified. Overall, findings contribute to our understanding of brain network disruption in cognitively intact pediatric-onset MS patients.

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List of Abbreviations

Abbreviation	Meaning
9HPT	Nine hole peg test
ADHD	Attention deficit hyperactivity disorder
BA	Brodmann area
Bil	Bilateral
CES-D	Centre for Epidemiologic Studies-Depression scale
CIS	Clinically isolated syndrome
CNS	Central nervous system
DLPFC	Dorsal lateral prefrontal cortex
DMN	Default mode network
DTI	Diffusion tensor imaging
EDSS	Expanded Disability Status Scale
fMRI	Functional magnetic resonance imaging
GNG	Go/No-go
L	left
MRI	Magnetic resonance imaging
MS	Multiple Sclerosis
PedsQL	Varni Pediatric Quality of Life Multidimensional Fatigue Scale
pre-SMA	Pre-sensory motor area
R	Right
RAVLT	Rey Auditory Verbal Learning Test

ROI	Regions of interest
RRMS	Relapse-remitting multiple sclerosis
SDMT	Symbol Digit Modalities Test
SMA	Supplementary motor area
SPMS	Secondary progressive multiple sclerosis

Introduction

To date, research has focused on the identification and characterization of cognitive impairment in pediatric-onset multiple sclerosis (MS). Studies have focused on understanding clinical and neural correlates of cognitive dysfunction in this population in order to better predict who is at risk of cognitive impairment. Less is known about how the developing brain may adapt to the disease processes that characterize MS. Given that MS is a dynamic disease that involves ongoing demyelination, remyelination, axonal loss, and cell death, a weak to moderate relationship exists between neuropsychological measures and structural magnetic resonance imaging (MRI) indices. Fluctuations in the appearance of lesions and changes in brain volume metrics associated with disease pathology likely contribute to these relatively weak relationships. Moreover, structural imaging does not provide information regarding functional brain changes that may occur during the course of disease.

The brain's potential to reorganize can be investigated using functional neuroimaging techniques. Indeed, the role of functional reorganization in the preservation of cognitive abilities has been documented in adults with MS, but has received little attention in children and adolescents who have MS. Thus, the goal of the current study is to use functional MRI techniques to explore whether neuroplasticity is observed on a simple inhibitory control task (Go/No-go task) for which we expect pediatric MS patients to perform at a behavioral level similar to healthy controls. We will test the hypothesis that patients with MS will show greater recruitment of frontal brain regions when performing this low cognitive load attention task relative to controls. This increased cortical recruitment is believed to represent compensatory mechanisms in the patient population.

Overview of Multiple sclerosis

Multiple sclerosis (MS) is a life-long inflammatory, demyelinating and neurodegenerative disease that can occur in childhood. The worldwide prevalence of MS is estimated at 50:100,000, with 2.7-5% (1.35-2.5:100,000) of these cases occurring before the age of 18 years, and about 0.2-0.7% (0.4-1.4:100,000) occurring during infancy and early childhood (Duquette et al. 1987; Ruggierir, Polizzi, Pavone, & Grimaldi, 1999; Yeh et al., 2009). In Canada, an incidence of pediatric-onset MS is found in 0.9 per 100,000 Canadians (Banwell, Ghezzi, Bar-Or, Mikaeloff, & Tardieu, 2007).

The disease process is characterized by inflammation and demyelination of the brain and spinal cord that lead to scarring known as “sclerosis”. This damage may lead to lesions preventing the transmission of nerve signals. Depending on the location and extent of these lesions, physical or cognitive deficits of varying severity may occur (Ghezzi et al., 2002). While demyelination is the most characteristic feature of MS, recent studies (Mesaros et al., 2008) show that neurodegenerative processes are also involved. Thus, damage extends beyond myelin and oligodendroglial cells and involves grey matter as well. Recent work in pediatric MS has shown substantial loss of both grey matter and white matter volume (Mesaros et al., 2008). Volume loss in the thalamus is particularly notable and can occur prior to observable volume loss in the whole brain (Kerbrat et al., 2012; Mesaros et al., 2008).

Some notable differences exist in terms of disease burden and MRI activity in pediatric patients as compared with and adult patients with MS. A study of 41 pediatric and 35 adult-onset MS patients examined MRI characteristics at time of first MS symptoms and at follow-up (Waubant et al., 2009). Results found that pediatric-onset MS patients had (1) a higher number of total T2 and larger T2-bright areas than adult-onset MS patients at initial scanning and(2) more T2-bright foci in the posterior fossa. Follow-up scans found that pediatric-onset MS

patients had more new T2-bright and gadolinium enhancing foci than adult onset. Thus, pediatric-onset MS patients not only had a higher disease burden but also had greater posterior fossa involvement and a higher rate of new lesions compared to adult-onset MS patients, controlling for disease duration. These differences in lesion location and activity may indicate differences in disease burden and clinical outcome in the two groups.

A relapsing-remitting course of disease is present in over 95% of children (Banwell et al., 2007). In relapsing-remitting MS (RRMS), patients experience acute and worsening attacks followed by subsequent periods of remission with either partial or complete recovery to pre-attack function. The time between attacks can range from months to years (Banwell et al., 2007).

Cognitive Impairment in Pediatric-Onset Multiple Sclerosis

Cognitive impairment occurs in 30-50% of children and adolescents with MS and may be severe enough to compromise intellectual functioning, academic performance, and daily life function (Amato et al., 2008; Banwell & Anderson, 2005; MacAllister et al., 2005; Till et al., 2011). Most studies report that cognitive deficits can be detected across multiple domains, including information processing speed, attention, episodic memory, language (receptive, verbal fluency, naming), as well as some aspects of visual-spatial and visual-motor function (Ghezzi, Goretti, Portaccio, Roscio, & Amato, 2010). Executive dysfunction is also demonstrated, particularly with regard to working memory and cognitive flexibility, whereas inhibitory control, as assessed on continuous performance tests, in general, is less compromised (Till et al., 2012). Children and adolescents with MS may also experience difficulty with functioning in a regular classroom, reduced participation in hobbies and sports, and may experience fatigue and affective disorders. All of these difficulties may contribute to social difficulties (Ghezzi et al., 2010).

Clinical correlates of cognitive impairment. Cognitive impairment in pediatric-onset MS patients has been associated with increased physical disability as assessed using the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983), a higher number of relapses, younger age at onset, and longer disease length (Banwell et al., 2007). Studies have shown that children with a younger age of disease onset, as opposed to a later age of disease onset, are more likely to experience cognitive dysfunction, particularly on tasks that require self-generated organizational strategies, efficient processing speed or working memory (Banwell & Anderson, 2005; MacAllister et al., 2005). Several hypotheses have been put forth to help explain the increased vulnerability of the developing brain. First, the combination of incomplete myelinogenesis and demyelination of the immature central nervous system may impair neuronal network formation, thereby increasing the risk of the cognitive impairment in patients with a young disease onset. Second, pediatric patients have less established skills at time of disease onset and developing skills may be more susceptible to disruption than established ones. Third, functional recovery or use of compensatory strategies may be restricted by the young child's limited repertoire of existing skills.

Younger age at onset is analogous to an adult patient with a low cognitive reserve. Cognitive reserve theory (Stern, 2002) states that individuals differ in their cognitive efficiency used to process information. An individual's cognitive reserve can be estimated by premorbid intelligence (often estimated by vocabulary knowledge) or by educational attainment. In MS, higher cognitive reserve serves to: (1) protect individuals from cognitive impairment that can result as a function of diffuse brain pathology; and (2) allow patients to perform on information processing tasks similarly to healthy controls (Sumowski, Chiaravalloti, Wylie, & DeLuca, 2009; Arnett, 2010; Benedict, Morrow, Guttman, Cookfair, & Schretlen, 2010). Adults with MS who have a higher education are more likely to display cognitive compensatory mechanisms (Bonnet,

Deloire, Salort, Dousset, Petry, & Brochet, 2006) and are better able to withstand acquired neuropathological changes than adult MS patients who have a lower level of education. Thus, an individual's level of cognitive reserve may serve to protect against neurocognitive decline secondary to the disease.

Children with MS -- as a result of their young age -- have less developed networks, which is analogous to having a low cognitive reserve in adulthood. Because the disease impacts children and adolescents during critical periods of brain development when knowledge and skills are being rapidly acquired, young onset of the disease may increase risk of cognitive impairment relative to an older onset of disease.

MRI correlates of cognitive impairment. MRI techniques have shown that reduced volume in the thalamus and in the entire brain is moderately associated with lower cognitive performance in pediatric-onset MS patients (Till et al., 2011). These findings suggest that pediatric-onset MS patients do not exhibit protective factors against the influence of MS on brain integrity. Moreover, the relationship between thalamic volume loss and reductions in global cognitive functioning, mental processing speed, visuomotor integration and expressive vocabulary suggests that the thalamus plays an important role in cognitive processes that require the integration of many brain regions. Similar associations between reduced thalamic size and global cognitive dysfunction have been reported in adults with MS (Riccitelli, Rocca, Pagani, Rodegher, Rossi, Falini, et al., 2011).

Normalized brain volume (i.e. corrected for head size) is considered to be a measure of overall brain health. In pediatric onset MS, a reduction in normalized brain volume has been documented (Kerbrat et al., 2012; Till et al., 2011), and this may reflect an overall failure of the brain to develop at an age appropriate rate. Reduction in cerebral volume has been associated with poorer performance on a measure of verbal learning and memory to the same extent as a

reduction in hippocampal volume (Fuentes et al., 2012). These findings suggest that both diffuse and focal pathology can contribute to learning and memory performance – consistent with the idea that learning and memory involve both cortical and subcortical brain regions.

Lesion volume is typically less strongly correlated with measures of cognition and physical disability, perhaps reflecting the poor anatomical specificity of this index of pathological damage (Rovaris et al., 1998). In other words, high lesion volume may not associate strongly with a clinical outcome if the brain regions affected are not related to the specific clinical outcome (i.e. a large lesion in the brainstem versus the frontal lobes will have different clinical outcomes), or it may be the result of many diffuse small lesions throughout the brain. A second reason why lesion volume may not be a robust correlate of cognition is because cognitive impairment can be found in the absence of lesioned tissue and instead reflect neurodegenerative processes that can also impact cognition (Rovaris, Comi, & Filippi, 2006). Thirdly, lesion volume may not strongly correlate with cognition since the neurons may merely be inflamed (as detected by T2-weighted imaging) rather than permanently damaged; thus, when the inflammation remits, the neurons may return to normal function (Miller, Grossman, Reingold, & McFarland, 1998).

Diffusion tensor imaging (DTI) is another type of quantitative neuroimaging method that is sensitive to detecting disruption to white matter microstructure in MS. This technique can be used to identify pathological changes in white matter before lesions or atrophy becomes visible (Rovaris et al., 2006). Studies have shown that reduced fractional anisotropy (a measure of white matter integrity) in the corpus callosum is associated with slower processing speed in adults with MS (Roosendaal et al., 2009) as well as children with MS (Bethune et al., 2011; Till et al., 2011).

Summary

Cognitive impairment is an important sequela of pediatric-onset MS. The extent of cognitive impairment appears to be moderately correlated with global and regional brain volume loss. Further work is required to understand other possible factors that may play a role in limiting the clinical expression of damage associated with the disease. Using functional MRI (fMRI) techniques, we may be able to uncover other factors that help to explain why some children are spared cognitive impairment despite the accrual of multiple lesions and loss of brain volume during the course of the disease. One possibility is that youth with MS rely upon functional reorganization of non-injured tissue to assume functions of damaged tissue. The capacity for compensatory strategies may explain why some developing executive functions, such as inhibitory control, do not show impairment in young individuals with MS. The next section will examine the functional neuroimaging literature conducted in patients with MS with a focus on brain activation patterns that are associated with “normal” behavioural outcomes in this population.

Relating brain damage to adaptive functional reorganization in patients with MS

Adaptive functional reorganization in patients with MS is defined as changes in brain neural pathways that permit the individual to perform similarly to pre-insult level. Studies have shown that cognitively preserved adult patients with MS recruit additional brain areas to perform tasks of memory and attention at the same level as healthy controls (Audoin, Van Au et al., 2005; Chiaravalloti et al., 2005; Bonnet, et al., 2010). The observed increase in brain activation is interpreted as a functional or neural compensatory mechanism since the brain must work harder (i.e. require more blood flow to new brain regions) to achieve the same level of behaviour. Of note, while overall behavioural performance in the patients does not significantly differ from

controls on these tasks, reaction time tends to be slightly slower (Audoin, Van Au, Ranjeva, Ibarrola, Malikova et al., 2005; Chiaravalloti et al., 2005; Bonnet et al., 2010).

The potential for functional reorganization appears to be limited by the brain's ability to recruit more brain regions (Schoonheim, Geurts, & Barkhof, 2010). As shown in Figure 1, the initial structural damage occurring early in the disease (i.e. Phase 1) is associated with a steep increase in the extent of hyperactivation in the brain. This increase represents a functional reorganization response to the structural damage and allows for preservation of cognitive functioning to occur. Evidence in support of functional reorganization in adults with MS is demonstrated by greater activation of brain areas (i.e. quantitative differences), as well as the recruitment of additional brain areas (i.e. topographic differences). These differences are described in detail in the next section.

Phase 2, as shown in Figure 1, refers to the extent of increased structural damage, which in turn, is associated with a stronger response in functional reorganization. Importantly, there is a finite capacity for the system's ability to demonstrate functional reorganization; in other words, the brain's ability to recruit additional regions reaches its peak once the extent of structural damage in the brain reaches a maximal threshold for functional reorganization. Because the capacity for functional reorganization is now limited, this is the point at which clinical disability becomes more pronounced.

In Phase 3, clinical disability becomes progressive with increasing structural damage and a decreasing capacity of the brain for functional reorganization. The inverse relationship between the severity of clinical disability and the degree of functional reorganization that is possible is referred to as the "disease progression hypothesis" (Schoonheim et al., 2010). According to this hypothesis, it is suggested that patients with MS who have mild cognitive impairment may be recruiting more brain regions to compensate; In contrast, those with severe cognitive impairment

are more likely to have increased structural damage in the brain, which in turn, results in a limited capacity of the brain to recruit additional 'healthy' areas for functional reorganization to occur (Schoonheim et. al., 2010).

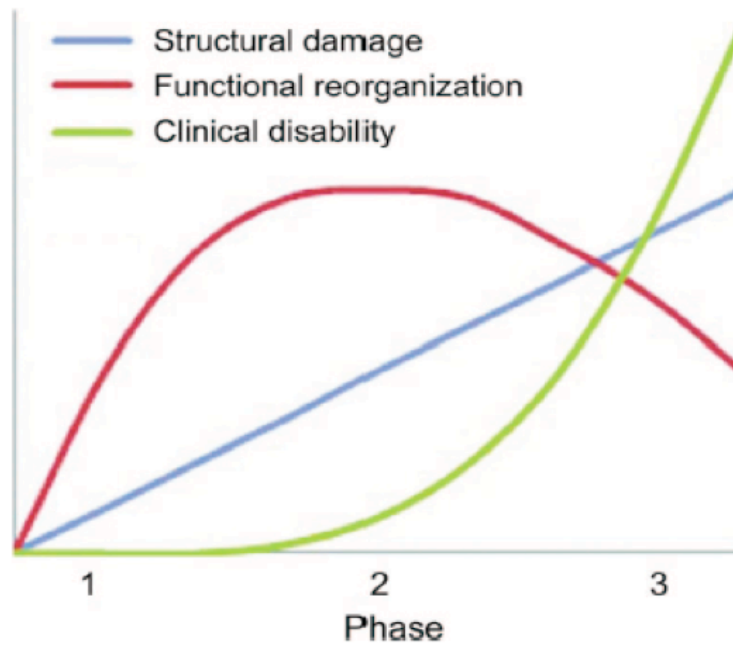


Figure 1. Multiple Sclerosis disease progression hypothesis (Schoonheim et al., 2010).

Initially, 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 1.

After functional reorganization reaches its peak in phase 2 and decreases thereafter, cognitive impairment and disability progressively develop throughout phase 3.

Evidence for the disease progression hypothesis in MS (Schoonheim et al., 2010) comes from a functional MRI study conducted in sixteen patients who were in the early stages of MS and had varying degrees of cognitive impairment (Hawellek, Hipp, Lewis, Corbetta, & Engel, 2011). The study examined how cognitive inefficiency (defined as a decrease in processing speed, executive functions and attentional control) is associated with MS-related changes in structural and functional connectivity in the default mode network (DMN), which is the network that is active during rest, and the control network, which refers to the network implicated in the deployment of attention and cognitive control (Hawellek et al., 2011). Functional connectivity provides information about how the brain is networked and what networks are activated when completing a given task. Thus, functional connectivity can be used to identify distinct functional networks that may be disrupted by diffuse pathology. Relative to healthy controls and to less cognitively impaired MS patients, the patients with low cognitive efficiency scores exhibited *increased* functional connectivity in the DMN and the control network. Consistent with the disease progression hypothesis, reduction in white matter volume (a marker of atrophy in the brain) was associated with a loss in cognitive efficiency and *greater* functional connectivity. Put another way, patients with cognitive impairment when compared to controls showed greater activation in both the default mode and cognitive control networks in the face of having greater structural damage (i.e. reduction in anatomical connectivity). This result is counterintuitive to the prominent view that a pathological loss in function is reflected through a loss of fluctuations in dedicated brain systems as seen in other neurological populations such as stroke (Carter et al., 2010). MS may differ from these other pathologies as a result of the diffuse impact it has on the white matter integrity and the CNS networks, which in turn may account for the counterintuitive results showing greater functional connectivity in the face of structural brain damage (Hawellek et al., 2011).

There is only one study to date that has examined the idea of compensatory cerebral recruitment in pedsMS (Rocca, Absinta, Ghezzi, Moiola, Comi, & Filippi, 2009). This study used a simple motor task involving repetitive flexion-extension of the last four digit fingers to examine the pattern of cortical activation associated with simple movement. Relative to age-matched controls, pediatric MS patients (all right-handed) showed increased activation of the left primary sensorimotor cortex during the performance of this simple motor task, indicating that patients have a greater need to recruit more areas in order to perform the same task as age-matched controls. A secondary objective of this study was to examine the relationship between the extent of T2-weighted lesion volume and the degree of movement-associated brain activation. Results showed that the increased activation of the primary sensorimotor cortex was moderately correlated with the extent of T2 lesion volume. These findings are consistent with the idea that greater cerebral pathology is associated with a greater need to recruit additional brain regions as a compensatory mechanism.

Summary

The relationship between severity of disease and the brain's potential to reorganize has been documented using functional neuroimaging techniques in both adult- and pediatric-onset MS. Consistent across the functional neuroimaging studies is a lack of between-group difference on the task that is being performed. It is important to compare groups on tasks for which the behavior is similar across groups, as differences between groups would make interpretation of functional brain data difficult, if not impossible. While functional neuroimaging has been used to assess the role of functional reorganization in the preservation of cognitive abilities in adults with MS, little work has been done in this area with children and adolescents who have MS. The next

section will focus on brain activation patterns that are associated with attentional control and response inhibition, a behaviour that is typically preserved in pediatric-onset patients with MS.

Attentional control and Response Inhibition

Attentional control involves the ability to selectively attend to stimuli over a period of time and response inhibition refers to the ability to inhibit unwanted responses. The ability to inhibit an unwanted response involves regulation and monitoring of one's actions so that goals are met. Attentional control also relies on working memory, especially in cases where the environment is rich with distracters and the individual is required to keep information in mind in order to be able to select, update, maintain and retrieve this information when needed (Redick, Calvo, Gay, & Engle, 2011). Difficulties with attentional control and response inhibition may be associated with impulsivity, lack of self-control, inability to finish tasks, and careless mistakes.

The developmental course of response inhibition begins as early as 12 months when the ability to inhibit certain behaviours and learn new responses is demonstrated. Around age 3, children are capable of inhibiting behaviours, but still make perseverative errors occasionally. Around age 6, children's speed and accuracy of impulse control improves, and by age 9, they are able to monitor and regulate their actions more effectively (Anderson, Jacobs, & Harvey, 2008). Along a similar time frame with response inhibition, working memory begins to emerge in infancy and consolidate in middle to late childhood. These maturational changes coincide with brain development – in particular the growth of the frontal lobes, which are necessary for both attentional control and response inhibition (Anderson et al., 2008; Davidson, Amso, Anderson, & Diamond, 2006).

Measurement of Attentional Control and Response Inhibition. Attentional control and response inhibition can be assessed using a variety of methods, including the Flanker task

(Gómez-Guerrero et al., 2011), Stroop task (Ikeda, Okuzumi, Kokubun, & Haishi, 2011), and the Go/No-go task. In the Go/No-go task, which is used in the current study, participants must respond as quickly as possible to the Go stimulus, but inhibit responding to a No-go stimulus. There are many different versions of the Go/No-go task, but the paradigm developed by Mostofsky et al. (2003) will be reviewed here because it relates to the methods used in the current study. This task has been used with children in the MR scanner and is considered a simple Go/No-go task because it only has two stimuli that require attention. Basically, the Go/No-go task requires the participant to discriminate between two stimuli. The “go stimulus” – a green spaceship - requires the participant to respond by pushing a button whereas the “no-go stimulus” – a red spaceship - requires the participant to withhold a button press. The discrimination of these simple stimuli (i.e. green vs. red spaceships) minimizes the influence of cognitive demands, such as working memory, thereby making it possible to study the systems involved in inhibition of a simple motor response (i.e. finger press) (Mostofsky et al., 2003). Task stimuli also have a familiar colour cue-response association (green for Go; red for No-go) thereby minimizing the influence of cognitive demands (Mostofsky et al., 2003). The task is weighted toward Go stimuli (using a 5:1 ratio) in order to build up a tendency to respond with a button press and to increase the effort required in inhibiting a response when a No-go stimulus is presented. Moreover, both types of cues (i.e. Go and No-go) are presented at a rapid rate, which serves to increase the demand on the system involved in attentional control.

A Go/No-go task is optimally presented as an event-related design in the scanner. In this type of design, the brain activation areas associated with a No-go stimulus response can be contrasted with baseline or Go stimulus trials. However, comparing the No-go stimulus response to the Go stimulus response is problematic since the two events (to respond or withhold a response) are not independent, and there may be overlapping activation patterns in making a

decision in both types of responses (Simmonds, Pekar, & Mostofsky, 2008). Another problem with comparing a Go versus No-go response is that one condition involves a motor response and the other does not. A better solution to understanding brain region activations specific to attentional control would be to compare a Go response (in a typical Go/No-go paradigm) against a simple button press to a paradigm that does not require visual discrimination and decision making.

A block design is a less optimal design because it is difficult to determine if the activation patterns reported are truly a result of attentional control (Mostofsky et al., 2003). The block design approach examines attentional control by contrasting a block with both Go and No-go stimuli to a block with only Go stimuli. This approach is based on the idea that by contrasting the mixed block with the Go stimulus block, it is possible to isolate activation areas specific for attentional control. However, a problem with this approach is that the two blocks may differ simply because the mixed block requires the participant to have a higher level of vigilance than the Go-stimulus block. The mixed block requires activation of multiple systems involved in the recognition of different cues and in making decisions about the appropriate response (Mostofsky et al., 2003), rendering the block design as a non-ideal method for assessing attentional control. A more optimal approach is to use an event-related design which characterizes the stimulus, delay period and response time as separate events. This approach, when timed appropriately with scanning time, provides the opportunity to observe neural activity based on a BOLD signal associated with the part of the event one is interested in (in the present study it involves withholding the response). By comparing No-go to baseline, one is examining the regions commonly associated with response inhibition. Comparing Go versus No-go to examine response inhibition may remove regions that serve an important role in response inhibition because they are also involved in response selection (Mostofsky et al., 2003).

Functional brain activation related to attentional control and response inhibition in healthy controls. Functional MRI studies using the Go/No-go task in healthy adult controls have furthered our understanding of the neural activity associated with attentional control and response inhibition. Importantly, the regions of activation in the brain differ depending on the phase of the task, type of response (i.e. “go” versus “no go”), as well as the type of task that is being used (i.e. simple versus complex Go/No-go task). For the purpose of the current review, activation related to simple Go/No-go tasks with right-handed responses will only be discussed. During the preparation phase, significant brain activation is observed in bilateral, diffuse regions including the left dorsal premotor, left lateral occipital, right ventral premotor, right fusiform gyrus, and the right anterior cingulate-sensorimotor cortex (Watanabe et al., 2002). Activation in these brain regions is related to the preparation for motor execution and increased attention required for visual discrimination. Specifically, the supplementary motor area (SMA) and premotor cortex play an important role in preparatory process of motion whereas the left occipital area and right fusiform gyrus play a role in colour and target discrimination. With regard to “no go” versus “go” responses, a right-lateralized network has been associated with response inhibition (i.e. to orient and prepare for the No-go response) whereas efficiency of responding to the “go” stimulus (indicated by shorter reaction time on go trials and a higher percentage of correct no-go trials) appears to involve a more left lateralized network (Hirose, Chikazoe, Watanabe, Jimura, Kunimatsu, Abe et al., 2012)

Recently, Simmonds et al. (2008) performed an activation likelihood estimate (ALE) meta-analysis of five studies examining the pattern of neural activation in healthy adults performing simple Go/No-go tasks (i.e. in which stimulus-response associations remained constant) and another five studies conducted using complex Go/No-go tasks (i.e. in which stimulus-response associations had to be manipulated based on information in working memory).

Using an event-related contrast of “No-go versus baseline”, regions that were common to successfully inhibited No-go stimuli across the five studies that used the simple Go/No-go tasks were then characterized. Result from this analysis associated successfully inhibited responses (not responding to the “no-go” stimulus) with a primarily right-lateralized network. The specific brain regions involved the right pre-SMA [Brodmann Area (BA) 6], right precuneus (BA 7), right inferior occipital gyrus (BA 19), and the left fusiform gyrus/posterior cerebellum (BA 19/37).

Previous human lesion studies and imaging studies lend support to the importance of the pre-SMA (also known as the superior medial wall) not only in motor preparation (responding to a Go stimulus) but also in response inhibition (withholding a response to a No-go stimulus). Poor inhibitory response is associated with lesions in the superior medial frontal lobe (Floden & Stuss, 2006; Picton et al., 2006). The pre-SMA is activated during response inhibition tasks (Bellgrove, Hester, & Garavan, 2004; Mostofsky et al., 2003), and motor response preparation and selection (Barber & Carter, 2005), whereas the left fusiform gyrus is a visual association area that has connections to the posterior parietal and prefrontal areas (Pandya & Seltzer, 1982), which may be needed to correctly recognize the cue or provide feedback whether to inhibit the response (Simmonds et al., 2008).

It should also be noted that activation differences are reported between correct and incorrect responses (errors of commission). Using a simple Go/No-go task whereby participants respond to a particular stimulus (“X”) and withhold responding to a different stimulus (“K”), Kiehl, Liddle, and Hopfinger (2000) report extensive activation in the rostral anterior cingulate cortex and left lateral frontal cortex when a commission error was made. These regions are implicated in error related processes and are thought to serve as the brain’s error monitoring system.

Functional brain activation related to attentional control and response inhibition in patients with MS. Several studies using the Go/No-go paradigm have reported differences in the regions and extent of activation demonstrated in patients with MS as compared with controls. In a sample of 15 patients with RRMS who were characterized by recent disease onset and 20 controls, Bonnet et al. (2010) examined performance on the Go/No-go paradigm using 4 conditions that increased in difficulty. The conditions included: (1) a *tonic alertness condition* where participants had to press a button every time they saw a figure on the screen; (2) a *simple Go/No-go condition* where participants had to respond to the target and withhold responding to the distracter; (3) a *reverse condition* where the target and distracter were reversed; and (4) a *complex Go/No-go condition* where there were 2 targets and 5 distracters. Results showed that patients performed the tasks as well as controls with the exception of the complex task on which patients were slower. Neuroimaging results showed that relative to controls, patients with higher performance (as measured by faster reaction times) had greater activation in the medial frontal gyrus. In the simple and complex conditions, cerebral activation patterns were greater in patients than controls thus implicating the involvement of distributed neuronal networks as a functional compensatory mechanism. The specific brain areas activated on each condition in patients compared with healthy subjects included the (a) left SMA, left cingulate gyrus, right dorsolateral prefrontal cortex (DLPFC), left occipital and temporal gyrus, left parahippocampal gyrus, left precentral gyrus, right cerebellum for the *tonic condition*; (b) right cingulate gyrus, right cerebellum, right temporo-occipital for the *simple Go/No-go condition*; (c) right DLPFC, left temporal lobule, bilateral superior parietal gyrus, and bilateral cerebellum for the *reverse Go/No-go condition*; and the (d) left thalamus, left temporo-occipital, right cingulate gyrus, right temporo-parietal, right temporal gyrus and the right cerebellum for the *complex Go/No-go condition*. Consistent with Phase 3 of the disease progression hypothesis, Bonnet et al. (2010)

found that patients with MS were unable to complete the complex Go/No-go task similar to controls when the cognitive load was so great that the cerebral compensatory mechanisms had become saturated. On the complex condition, patients exhibited a collapse of supplementary cerebral recruitment (as shown on the simple Go/No-go condition) and significantly longer reaction times compared with controls. Another important finding was that patients recruited medial frontal regions that were not recruited by controls. A final result of this study was that a higher degree of tissue damage was significantly correlated with greater activation in frontal regions. The more diffuse the tissue abnormalities (as assessed using lesion load and magnetization transfer ratio metrics of normal appearing brain tissue), the greater the frontal activation. This tendency to recruit higher-level decision making areas, including the prefrontal regions, suggest changes in strategies to compensate by patients with MS who suffer from widespread pathology in the brain.

In a recent study by Loitfelder et al. (2011), Go/No-go task performance was compared between healthy controls and three patient groups: those with clinically isolated syndrome (CIS), RRMS, and secondary progressive multiple sclerosis (SPMS). Patients with CIS are described as having a first neurological episode that results from inflammation/demyelination in the CNS and these individuals may or may not develop MS, whereas SPMS is one of the four recognized forms of MS and is characterized as a steady progression of neurological damage that may contain relapses with only minor remissions (Rog et al., 2010). Results showed varying activation levels depending on the severity of brain damage. More specifically, patients with CIS (who characteristically have the least amount of brain insult compared to the other clinical groups) demonstrated no difference in activation patterns when compared to controls. In contrast, patients with RRMS when compared to patients with CIS had a relative increase in activation patterns in the precuneus, both superior parietal lobes, and the right fusiform gyrus --despite

similar cognitive profiles. Taken together, these findings indicate compensatory strategies amongst the patients with more diffuse brain insult, but not amongst the CIS patients who are not characterized by diffuse brain insult. Patients with SPMS in comparison to patients with CIS had the worst neuropsychological performance and the most abnormal activation patterns as indicated by activation in diverse frontal and parietal regions. These findings lend further support to the idea that compensatory neuronal activation exists, but only to a certain point. Once the neuronal damage exceeds this threshold, an increase in neuronal recruitment pattern is no longer beneficial.

In another study by Smith et al. (2009), ten cognitively impaired adult patients with MS and ten healthy controls performed a Go/No-go task while in the scanner. Results showed that the MS patients performed significantly worse than controls in the ability to inhibit responses as indicated by a higher number of commission errors. Correlational analysis indicated that those with slower reaction times also had a lower degree of cognitive flexibility as measured by the Wisconsin Card Sorting Task. Results showed that patients had more neuronal activity than controls in the fusiform gyrus, cingulate gyrus, anterior cingulate, insula, putamen and cerebellum, with less activity than controls in the left supramarginal gyrus. Despite over-activation of several key brain regions, these patients were not able to achieve the same level of performance as controls. An explanation for why the over activation of brain regions was not associated with better performance in this study may be because these patients were more impaired cognitively relative to prior studies where the MS sample were either early in the disease process or were characterized as having minimal to no cognitive impairment. Another difference to explain why task performance of these patients was poor may relate to the finding showing reduced activation in the left supramarginal gyrus. This region is involved in sensory feedback during motor tasks and in awareness of errors (Hester, Foxe, Molholm, Shpaner, &

Garavan, 2005), suggesting that patients were not aware of their mistakes. Finally, it is possible that recruitment of more frontal brain regions, such as the dorsolateral prefrontal cortex (DLPFC), is needed for improving performance on the task.

Studies examining response inhibition using Go/No-go offer mixed results in terms of task performance and degree of brain activation. Studies where there is little cognitive impairment found in patients compared to healthy controls report *increased* degree of activation as being beneficial to supporting similar task performance (Bonnet et al., 2010). Mixed results come from studies reporting diffuse damage, where some studies report increased brain activation patterns as being beneficial to task performance (Loitfelder et al., 2011) whereas others report an over-activation of brain regions as not benefiting task performance (Smith et al., 2009). Although literature examining the idea of cerebral compensatory strategies in adult MS is growing, the relationship between increased brain activation and better task performance in patients with cognitive impairment remains unclear.

Purpose

Studies have shown that response inhibition is rarely compromised in adult patients with MS (Bonnett et al., 2010) as well as children and adolescents with MS (Till et al., 2012). Using functional MRI techniques, we can better understand why this executive function remains relatively preserved in pediatric-onset MS patients, despite frequent impairment in other cognitive domains, such as processing speed and attention, at early stages of the disease (Till et al., 2012; Till et al., 2011). If we identify differences in the activation patterns of patients compared with controls when performing a simple Go/No-go task that requires inhibitory control, we will improve our understanding of potential neuroplastic mechanisms that these young patients may use to maintain age-appropriate inhibitory control. These findings would

provide evidence suggesting that the developing brain is capable of using functional reorganization as an adaptive mechanism to offset impairment in this important executive function. The specific objectives and hypotheses of the proposed study are as follows:

Objective 1. To examine response inhibition in pediatric-onset MS patients and age-matched controls using a simple Go/No-go task

Consistent with the neuropsychological literature in pediatric-onset MS (Till et al., 2012), we do not expect cognitively intact pediatric-onset patients with MS to demonstrate deficits on the simple Go/No-go task with respect to accuracy and reaction time.

Objective 2. To evaluate the influence of age at disease onset and cerebral tissue damage on Go/No-go performance parameters

Given that attentional control and response inhibition networks continue to develop throughout childhood and into adolescence, it is hypothesized that younger age at disease will be associated with poorer performance on the Go/No-go task. Moreover, MRI metrics of cerebral tissue damage, including lesion volume, brain volume and thalamic volume, are expected to be weak to moderate correlates of reaction time and accuracy on the Go/No-go task given prior literature examining the association between structural MRI metrics and measures of cognitive performance.

Objective 3. To examine whether cognitively intact childhood-onset MS patients produce a less efficient pattern of cerebral activation compared with age-matched healthy controls

Using a whole brain approach, we hypothesize that pediatric-onset MS patients will recruit supplementary cerebral areas in addition to greater activation in expected brain regions when performing a simple Go/No-go task as compared with healthy controls.

Method

Participants

The initial sample consisted of 21 pediatric-onset relapsing remitting MS patients and 18 healthy controls between the ages of 14 and 25. Patients were recruited from the Pediatric Demyelinating Clinic at the Hospital for Sick Children. Patients were informed about the study by letter, followed by a phone-call by a research assistant. Healthy controls were recruited from the Undergraduate Research Participant Pool (URPP) at York University and from local advertisements. Patients and controls were matched on sex and age (± 12 months), with the exception of one matched pair for whom the control was 21 months older than the matched patient. Another three patients were not matched with a control participant, but were included in the analysis to increase the sample size.

The Research Ethics Board at York University and the Hospital for Sick Children approved the study. Participants older than 16 years provided informed consent, while younger participants gave verbal assent and their parents provided informed, written consent.

Inclusion/Exclusion Criteria

Patients were clinically stable at the time of evaluation; all patients were less than 4 weeks from any MS-related relapse or less than 4 weeks from corticosteroid treatment. Participants were excluded with the following criteria: (1) history of significant head trauma, as defined by a loss of consciousness for more than 5 minutes and a Glasgow scale score of less than 13; (2) history of alcohol or illicit drug use (greater than once per week, or use of cocaine, heroin or other illicit drugs); (3) best corrected visual acuity less than 20/100 in both eyes and self-reported red/green colour blindness; (4) hemiparesis of the dominant arm; (5) non-English speaking; (6) cognitive or behavioural disturbance which is considered to be severe enough to

preclude compliance with study procedures (disturbance may be secondary to a psychiatric disorder, such as ADHD). Patients with a history of a mood-related disorder (e.g. depression) were included since mood-related symptoms may be secondary to the MS disease process. Healthy control participants met the same inclusion and exclusion criteria, except those related to MS.

General Procedure

Participants were first screened by telephone or, for patients, in clinic using a screening form (see Appendix 1) to ensure inclusion and exclusion criteria were met. Prior to testing, participants completed the MRI screening form to ensure they were safe to go inside the scanner. On the day of testing, participants completed questionnaires about demographics, mood, fatigue, as well as a 60-minute neuropsychological battery (see Table 1). Prior to scanning, participants were trained on the Go/No-go task (for 1 minute with 22 stimuli presented) to ensure understanding and comfort with the task demands. Participants then underwent magnetic resonance imaging (MRI) using a 3.0 Tesla Siemens Tim Trio scanner at York University. The total time for MRI scanning was 70 minutes for healthy controls and 90 minutes for MS patients.

Measures

Clinical-Demographic Information. All participants completed questionnaires about: (1) general health and demographic information using a Case History Form (see Appendix 2); (2) handedness using the Dutch Handedness Questionnaire (Van Stein, 1992); (3) mood using the Center for Epidemiologic Studies Depression Scale (CES-D) (Faulstich, Carey, Ruggiero, Enyart, & Gresham, 1986); and (4) fatigue on three dimensions (General, Cognitive, Sleep/Rest) using the Varni Pediatric Quality of Life (PedsQL) Multidimensional Fatigue Scale: Young adult self-report (ages 18-25) or Teen self-report (ages 13-18) (Varni, Seid, & Rode, 1999). Raw

scores were used for the CES-D and for each fatigue dimension and for total fatigue score on the PedsQL. An estimate of socioeconomic status was determined based on parental education and occupational status using the validated Barratt Simplified Measure of Social Status (Barratt, 2006). For patients with MS, clinical information was obtained via chart review (or communication with their neurologist) regarding the following outcomes: age at disease onset (defined by age at first MS attack), total number of relapses, medication use, and physical disability as assessed by a neurologist using the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) within three months of this study.

Neuropsychological battery. All participants were evaluated with a battery of clinical neuropsychological tests that has been validated for detecting disease-related cognitive problems in childhood MS (see **Table 1** for test battery and dependent variables). These measures were used to characterize the cognitive profile for the two groups and to compare cognitive functioning to performance on the Go/No-go task. All of the neuropsychological data were analyzed after z transformation.

Full scale IQ was determined using the Wechsler Abbreviated Scales of Intelligence (WASI) two-subtest estimate (Wechsler, 1999). Attention and speed of processing were assessed using the Symbol Digit Modalities Test (SDMT) (oral version) (Smith, 1991), Woodcock Johnson (WJ-III) Decision Speed and Auditory Working Memory subtests (Woodcock, McGrew, & Mather, 2001), and the Trail Making Test (Parts A and B) (Reitan, 1959). Verbal learning and memory were assessed using the Rey Auditory Verbal Learning test (RAVLT) (Lezak, 1983). The 9 Hole Peg Test (9HPT) (Mathiowetz, Weber, Kashman, & Volland, 1985) was used to examine fine motor dexterity and to rule out the possible confound of motor impairment on the Go/No-go task. Norms for the 9HPT were taken from the National Institute of Health (NIH) normalization cohort (Wang et al., 2011). These norms were chosen because

they are based on an age and sex-matched sample of large size that is similar to the participants in the present study. Of note, the 9HPT was originally only administered to the patient group (to rule out motor impairment in the dominant hand) and hence data for the controls were not available.

Table 1

List of cognitive and neuropsychological measures

Domain	Measure	Dependent Measure	Estimated time
Motor Function	9 Hole Peg Test	Time (z-score)	4 min
Intellectual Function	Wechsler Abbreviated Scales of Intelligence (WASI) – two subtest estimate of Full Scale IQ	<u>Vocabulary</u> to assess general word knowledge; <u>Matrix Reasoning</u> to provide a measure of nonverbal conceptual reasoning (z-score)	10 min
			8 min
Focused Attention and Cognitive Flexibility	Trail Making Test – Parts A and B; WJ-III: Auditory Working Memory	Time (z-score) Total score (z-score)	5 min
Speed of Processing	Symbol Digits Modalities Test (SDMT: oral version); WJ-III: Decision speed	Total score (z-score) Total score (z-score)	2 min
Learning & Memory	Rey Auditory Verbal Learning Test (RAVLT)	Total words recalled over 5 trials (z-score) Short and long delay recall score (z-score)	10 min
Fatigue	PedsQL – Multidimensional Fatigue Scale	Young Adult Report (ages 18-25); Teen Report (ages 13-18) (raw score)	4 min
Family socioeconomic status (SES)	The Barratt Simplified Measure of Social Status Measuring SES	Level of school completed (for mother & father); Occupation (for mother & father) (total score)	2 min
Mood	Center for Epidemiologic Studies Depression Scale (CES-D)	Total score (raw score)	4 min
Handedness	The Dutch Handedness Questionnaire	Total score for right, left, both hands	3 min

Note. The total time to complete all measures was 60 minutes. WJ-III = Woodcock-Johnson III. PedsQL= Varni Pediatric Quality of Life Multidimensional Fatigue Scale.

Go/No-go fMRI task

The Go/No-go task was programmed and run using E-prime (Psychological Software Tools, Pittsburg, PA, USA) on a Windows XP laptop. The program was originally developed by Mostofsky et al. (2003) and shared with our group for the current study. During the training period (outside the scanner), written instructions appeared on the computer screen and were read aloud by the research assistant. Participants were instructed to focus on the centre of the screen and push a button with their right index finger via a response keypad as quickly as possible when a green spaceship (Go stimulus) was presented on a black computer screen, but not when a red spaceship appeared (No-go stimulus) (see **Figure 2A for sample stimuli**). The spaceships were presented one at a time in a pseudo-random order over a brief, practice period (approximately 5 minutes). Each trial consisted of a spaceship presented for 200 ms followed by a 1300 ms inter-stimulus interval where a crosshair is displayed on the screen (see **Figure 2B**). The order of stimulus presentation favors a 5:1 green to red spaceship ratio in order to maximize the tendency for the participant to respond with a “go” button press. The following constraints were used: the red stimulus did not appear immediately after a rest interval or at data acquisition onset. When no stimulus was present, participants were asked to focus on the crosshair. Stimuli order did not differ across participants.

The same instructions and procedures were followed inside the scanner. However, the length of the task was longer (8 minutes). During the test session and while in the scanner, 150 trials were presented over 2 blocks, each consisting of 75 trials. Between each block, there was a brief rest interval lasting 20 seconds at which time three asterisks appeared on the screen and the participant was not required to make any motor response.

Performance parameters. The number of correct responses following stimulus presentation determined accuracy. A correct response was defined as a button press when a green

spaceship appeared (with a reaction time ranging between 200 to 460 milliseconds) and withholding a button press when a red spaceship appeared. A minimum accuracy rate of 75% correctly discriminated stimuli on the practice trial was accepted as an indication that the participant understood the task. A commission error was defined as a button response that occurred following the presentation of a red spaceship (No-go stimulus) or when a response was committed in less than 200 milliseconds following a go stimulus given that to make a basic perceptual decision and respond with a motor response it takes visual system and motor system around 200 milliseconds (Joubert, Rousselet, Fize, & Fabre-Thorpe, 2007). Omission error was defined as an absence of a button response following the presentation of the green spaceship (Go stimulus).

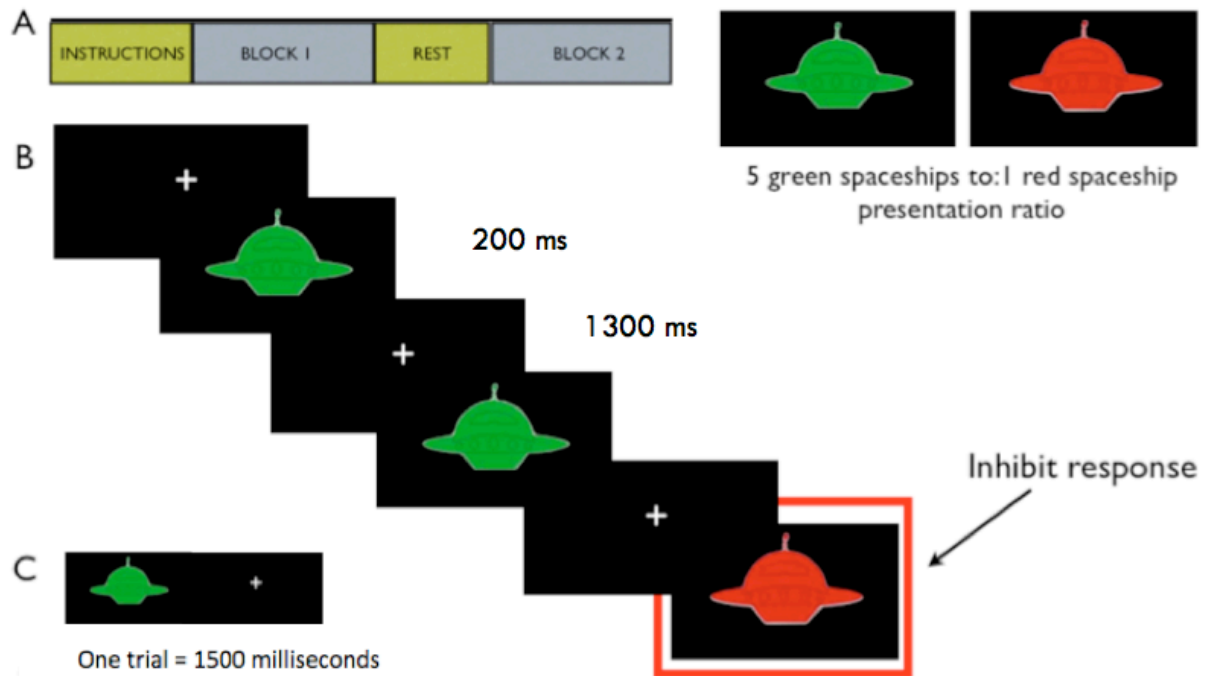


Figure 2. Schematic of Go/No-go paradigm.

A. Task design. B. Example of presentation sequence. C. Example of one 'go' trial.

MRI Procedures

Structural MRI Acquisition. Scans were carried out at the Neuroimaging Facility of the Center for Vision Research at York University 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. Participants responded to the tasks by pressing keys on a MRI compatible keypad (Current Designs, CA) with their index and middle fingers of their right hand. Foam padding was used to comfortably secure the participant's head in the head-coil, and to minimize head motion during scans.

A high-resolution structural volumetric image was acquired from all participants using a T1-weighted three-dimensional MPRAGE sequence (1 mm isotropic voxel size, TR=2300 ms, TE=2.96 ms). Proton density-weighted (TR=2200 ms, TE=10 ms, turbo factor=4) and T2-weighted (TR=4500 ms, TE=83 ms, turbo factor=11) images were acquired for lesion segmentation using 2D turbo spin-echo sequences with $1 \times 1 \times 3 \text{ mm}^3$ voxel size, along with a matching 2D turbo FLAIR sequence with TR=9000 ms, TE=88 ms, TI=2407.5 ms.

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

The following methods were used: First, a preprocessing routine was run 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 & 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 (Francis, 2004) 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 white matter. Supratentorial and infratentorial lesion volumes were combined as a measure of total brain lesion volume.

Brain and thalamus segmentation. Three standard preprocessing steps were applied to the native T1-weighted images to delineate whole brain and thalamus. These included: (1) removing noise by using the optimized non-local means filter (Coupe et al., 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, Zijdenbos, & Evans, 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 preprocessed T1-weighted images of each time point were then linearly registered to a subject-specific linear template created using the principles of unbiased average template construction as described in (Fonov et al., 2011). A hierarchical nine-parameter linear registration based on intensity cross-correlation as a similarity measure was performed between the subject-specific linear template and the ICBM152 population template (Collins, Neelin, Peters & Evans, 1994) to align the subject-specific template with the population template in stereotaxic space.

Native T1-weighted images were resampled once via the concatenated transformation from native space to the subject-specific template space, and from the subject-specific template space to the ICBM152 population template space. A multi-resolution non-local patch-based segmentation technique was used to extract the brain in the T1-weighted images resampled into the ICBM152 template space, using BEaST with a library of priors (Eskildsen et al., 2012). As T1-weighted images of each time point were also registered to a non-linear subject-specific template that was non-linearly registered to the population template (Collins et al., 1994), the thalamus label defined on the ICBM152 population template was warped back onto each time point's T1-weighted images using the concatenated transformations, thus segmenting the thalamus in each scan for each subject.

Functional MRI Acquisition

Functional MRI images were acquired using a T2*-weighted echo planar imaging (EPI) sequence (TE=30 ms, flip angle=90⁰, matrix size 86x64, FOV=258x192mm, TR=2s). Thirty-four 4 mm thick axial slices acquired in transverse orientation allowed for coverage of the whole brain.

Image Pre-processing and Data Analysis

Pre-processing and data analyses were performed using FSL software (Smith et al., 2004). First, DICOM (Digital Imaging and Communications in Medicine) images were converted to NIFTI format (*dicom2nift*). Second, non-brain tissue (skull and scalp) from the images of the whole brain was removed using Brain Extraction Tool (BET2) (Smith, 2002; Jenkinson, Pechaud, & Smith, 2005). Fourth, a first level analysis was carried out by constructing voxel-wise *t*-maps for each subject using the following steps: (a) *Data*: Each subject's data contained 210 volumes with a TR of 2 seconds; 4 volumes were deleted from the

beginning of the run resulting in 206 volumes. A high pass temporal filter cutoff of 60 seconds was implemented to remove low frequency artifact in each voxel's time series. *(b) Pre-Stats:* Spatial smoothing of the functional time series was done using a Gaussian filter (full width half maximum (FWHM) = 5 mm) to account for anatomic variability making the effective resolution coarser. This step is intended to reduce noise without reducing valid activation. *(c) Stats:* In this step, the general linear model that models the expected hemodynamic response was set up. FILM prewhitening was used to improve the linear model. FILM uses a robust and accurate nonparametric estimation of the time series autocorrelation to prewhiten each voxel's time series, thus providing an improved estimation efficiency. Six standard motion parameters were also accounted for in the model (3 rotational (pitch, yaw, roll and 3 translational (x, y, z) motion parameters) in order to re-align all of the volumes to the first volume. The full model setup was used to account for the two explanatory variables (Go and No-go), though for the current study, only No-Go trials were modeled. The shape of each explanatory variable was accounted for by the onset time and the duration and this was convolved with the Double-Gamma Hemodynamic Response function (HRF). Double-Gamma HRF attempts to match the difference between the stimulus waveform and the hemodynamic response function. A temporal derivative was added, which shifts the waveform slightly in time in order to achieve a better fit to the data by reducing unexplained noise and thus increasing power to detect statistical significance. A contrast (0,1) was set up to see which voxels showed any difference in BOLD response during presentation of a No-Go stimulus relative to baseline modeled in step c. *(d) Post-Stats:* Significant activations were only provided for those values that were greater than threshold (cluster threshold, which corresponds to a Z threshold of 2.3 ($p < 0.05$)). *(e) Registration:* In order to summarize the location of activated voxels using coordinates from the MNI, the T1 anatomical scan was incorporated and coregistered to the MNI152 1mm brain template using linear registrations

(12DOF). Finally, a third level analysis was conducted. Thirty-seven COPE images were inputted into the model. These are the images for the No-go response. Analyses involved between group (controls vs. patients), non-paired contrasts. In addition, healthy controls and patients were analyzed separately to examine within group activation. Significant activations were only provided for values that were greater than the cluster threshold (i.e. Z threshold of 2.3, $p < 0.05$).

Table 2

Areas of activation for the No-go response on simple Go/No-go tasks as performed by healthy controls (Simmonds et al., 2008) and patients with MS (Bonnet et al., 2010)

Participants	Brain Region	Hem.	BA
Healthy Controls	Inferior occipital gyrus	R	19
	Fusiform gyrus/posterior cerebellum	L	19/37
	Superior medial wall (pre-SMA)	R	6/32
	Precuneus	R	7
Patients with MS	Cingulate gyrus	R	31
	Cerebellum Hemisphere	R	-
	Temporo-occipital	R	-
	Cingulate gyrus	R	24
	Temporal gyrus	R	21/22
	Medial frontal gyrus	L	9

Note: Hem.=Hemispheres, B=Bilateral; BA = Brodmann Area; SMA = Supplementary Motor Area.

Statistical Analysis

The Kolmogorov-Smirnov and Levene's tests were used to assess for any violations of normality and homogeneity of variance within data sets. Groups were compared on demographic (age, sex, socioeconomic status, fatigue, mood) and neuropsychological variables using independent *t*-tests or Mann-Whitney *U* tests, where appropriate. In the absence of a normal distribution, nonparametric tests were used. Cognitive impairment was determined if participants scored below 1.5 standard deviations on at least 2 of 8 tests. The tests included: (1) WASI Matrix Reasoning; (2) WASI Vocabulary, (3) Trail Making Part A and B; (4) WJ-III Auditory Memory; (5) SDMT; (6) WJ-III Decision Making; and (7) RAVLT (total learning). All behavioural analyses were performed using SPSS 20 (IBM, 2011). A conservative alpha of 0.01 was used to assess significance in the between-group analysis of the cognitive data because of multiple comparisons involved; for all other analyses, an alpha of 0.05 was used.

Go/No-go task analysis (Objectives 1 and 2). The primary dependent variables for this task included accuracy (proportion correct across total go and no-go trials) and reaction time (RT). Reaction time below 200 ms was removed from the calculation of mean RT as a response below this threshold was considered a commission error. Likewise, a failure to respond to a target (i.e. an omission error) was not included in the calculation of mean RT. Secondary dependent variables included total number of commission (unsuccessful inhibition of response) and omission errors (required response not given to a Go stimulus). To assess differences between groups on the Go/No-go task, one-way analysis of variance and Kruskal-Wallis test were performed on each dependent variable. Pearson correlations (one-tailed) were used to assess the inter-relations between accuracy and RT on the Go/No-go task and clinical-demographic variables (age at assessment, age at disease onset, duration of disease, fatigue score, and depression score), and MRI variables (brain volume and thalamic volume, log-

transformed T2- and T1-weighted lesion volume). The relationship between age at disease onset and Go/No-go performance was examined after controlling for disease duration as to not confound younger age at disease onset with a longer disease duration. Note that T1- and T2-weighted lesion volumes were log transformed given the positively skewed distribution of these data. Spearman rank correlations were used for CES-D Depression total and PedsQL total fatigue scores given the non-normal distribution of these variables.

Functional MRI data analysis (Objective 3). A mixed effects: FLAME1 higher level modeling will be used to contrast voxels between patients and controls. This method uses Bayesian modeling and estimation. FLAME1 provides the most accurate estimation of activation. First, the higher-level model is fit and approximations are made regarding the activations. Then, all voxels that are close to threshold are processed using Mixed Effects variance (Metropolis-Hastings Markov Chain Monte Carlo sampling) to give a distribution for higher-level contrasts of parameter estimates, to which a general t-distribution is then fit. Functional whole brain activation data in response to the No-go stimulus was examined using FSLview (Smith et al., 2004). Activation patterns were defined for both groups as well as between groups for the No-go trials using Talairach Daemon function.

Group Characterization

From the initial sample of 18 control participants, one participant was excluded because of extreme motion artifact on the images due to repeated removal from the scanner as a result of discomfort, and very low performance outcomes on all cognitive measures that fell outside the normal range expected for control participants. From the original sample of 21 patients, one participant was removed due to technical error in acquiring behavioural data during the GNG task. Thus, clinical and neuroimaging data were available for 17 controls and 20 patients.

Demographic Information. As shown in Table 3, the healthy control group ranged in age from 14.92 - 24.33 years ($M = 19.26$, $SD = 2.63$) and the patient group ranged in age from 13.17 - 24.25 years ($M = 19.36$, $SD = 2.99$). There were no differences in age, social economic status, and in years of education. Both groups showed right hand dominance with 94% controls ($n = 16$) and 85% patients ($n = 17$) classified as right hand dominant. Seventy-six percent of controls ($n = 13$) and 70% of patients ($n = 14$) were female, consistent with the female sex predominance in MS post-puberty.

Clinical Features of the MS Group. The average age at disease onset (defined by date of first attack) was 13.60 ± 2.58 years of age (range: 10 - 19 years). The average disease duration was 5.07 ± 3.10 years, with a range of 1.10 - 10.92 years. The total number of relapses documented in the patient health records ranged from 1 to 10 with a median score of 3 relapses; only 7 patients experienced 5 relapses or more. Sixteen of 20 (80%) patients were receiving disease-modifying treatment at time of evaluation. Treatments included: Copaxone ($n=6$, 30%); Tysabri ($n=3$, 15%), Fingolimod ($n=2$, 10%); and interferon-beta: Avonex ($n = 4$, 20%); Betaseron ($n = 1$, 5%). The majority of patients (17/20; 85%) had a low grade of disability as characterized by an EDSS score below 3 ($Mdn = 1.5$, range: 1.0-6.0); only 3 of 20 patients (15%) had an EDSS score above 3 (which is still indicative of mild disability), and none of them required ambulatory aid and all had normal functioning of the right upper limb.

As shown in Table 3, mood as assessed by the CES-D scale, did not differ between the two groups using mean symptom count score. Mild symptoms of depression (as classified by a score between 16-26 points on the CES-D) were reported by 4 controls and 3 patients, whereas more elevated symptoms of depression (classified by a score above 27 points) were reported by 1 control and 5 patients. The MS group did not report more fatigue symptoms on the Total Fatigue scale as compared with controls. Fatigue symptoms did not differ between groups on any of the

individual fatigue scales of the Varni PedsQL (General Fatigue, Cognitive Fatigue and Sleep/Rest Fatigue scales), however General Fatigue scale was slightly higher in the MS group and approached significance ($p < 0.10$).

Structural MRI Measures. As shown in Table 4, controls and patients significantly differed with respect to normalized brain volume ($p = 0.003$). Thalamic volume approached significance ($p = .06$) with a larger volume in the controls relative to the patients. In the patient sample, the T2- and T1-weighted lesion volumes were log transformed as a result of outliers that skewed the data in a positive direction. For patients, mean log T2-weighted lesion volume was $0.95 \pm 0.21 \text{ cm}^3$ with a range of 0 to 2.01 cm^3 and mean log T1-weighted lesion volume was $0.58 \pm 0.13 \text{ cm}^3$ with a range of 0 to 1.87 cm^3 .

Table 3

Clinical and demographic information for healthy controls and patients with MS.

Measure	Healthy Controls n=17	Patients n=20	<i>p</i> value
Mean age (years)	19.26 (2.63)	19.36 (2.99)	0.91
Handedness (N, %R)	16 (94%)	17 (85%)	0.37 [†]
Social Economic Status	38.39 (14.40)	44.85 (14.59)	0.20*
Sex (N, %F)	13 (76%)	14 (70%)	0.66
Education (years)	13.18 (2.10)	13.2 (2.71)	0.97
Depression Score (CES-D)	12.35 (7.83)	16.55 (14.43)	0.73*
PedsQL-Total Score	23.59 (8.47)	30.35 (13.83)	0.17*
PedsQL-General Fatigue	6.82 (3.83)	9.50 (5.34)	0.09
PedsQL-Cognitive Fatigue	7.94 (3.79)	10.00 (5.86)	0.22*
PedsQL-Sleep/Rest Fatigue	9.47 (3.48)	10.85 (3.96)	0.27

Note. R = right handed; F = female; MS = multiple sclerosis; CES-D = Centre for Epidemiological Studies Depression Scale; PedsQL= Multidimensional Fatigue Scale. *P* values represent group differences using t-tests, *Mann-Whitney U tests, or [†]Chi-square analysis. Data are reported as mean and standard deviation, except where indicated.

Table 4

MRI measures for healthy controls and pediatric-onset MS patients

Measure	<u>Healthy Controls</u> n=17	<u>Patients</u> n=20	<i>p</i> value
Normalized Brain volume (cm ³)	1614.09 (75.57)	1546.47 (52.79)	0.003
Thalamic volume (cm ³)	12.57 (1.12)	11.79 (1.31)	0.06
Log T2-weighted LV (cm ³)	-	0.55 (0.95)	-
Log T1-weighted LV (cm ³)	-	0.47 (0.58)	-

Note. All data are reported as mean and standard deviation (M(SD)). LV = lesion volume.

Cognitive measures. Table 5 summarizes the cognitive measures for controls and patients. No significant difference was found in intellectual functioning between groups as measured by WASI Full scale IQ. Scores for controls and patients range from 81-124 and 78-129, respectively. Moreover, there were no statistical differences between groups on any of the specific cognitive measures included in the battery. Two patients and two controls met criteria for cognitive impairment using the pre-determined criterion of falling below 1.5 standard deviations on 2 of 8 measures in the screening battery. Importantly, the correlation between reaction time on the Go/No-go and z-score on 9HPT was not significant in the MS group ($r = -0.127, p = 0.59$), suggesting reduced fine motor dexterity on the 9HPT task was not associated with response speed on the Go/No-go task.

In summary, controls and patients did not differ in terms of demographic, clinical, cognitive and behavioural characteristics. Regarding the MRI variables, patients showed lower brain volume ($p < .01$) and thalamic volume ($p = 0.06$) as compared with the control group.

Table 5

Cognitive outcomes (Mean and SD) for healthy controls and pediatric-onset MS patients

Measure	Healthy controls	Patients with MS	Per cent < 1.5 SD		<i>p</i>
	n=17	n=20	HC	MS	
WASI-Full-2 IQ [†]	0.40 (0.78)	0.32 (0.75)	0	0	0.77
WASI Matrix Reasoning [†]	.41 (0.55)	0.22 (0.80)	0	1	0.47
WASI Vocabulary [†]	0.39 (0.69)	0.35 (0.86)	0	1	0.87
Trail Making Test-Part A [†]	0.49 (0.78)	0.41 (0.68)	0	0	0.74
Trail Making Test-Part B [†]	-0.09 (1.26)	0.24 (1.87)	11.76	15	0.81*
WJ-Decision Speed [†]	0.05 (1.23)	-0.09 (0.85)	5.88	5	0.70
WJ-Auditory Memory [†]	0.36 (0.63)	0.44 (0.51)	0	0	0.71
SDMT [†]	0.21 (1.25)	0.56 (1.38)	0	10	0.31*
RAVLT-total learning [†]	-0.56 (1.30)	-0.04 (1.21)	25.53	10	0.21
RAVLT-short delay	-0.73 (1.86)	-0.55 (2.35)	23.53	20	0.40*
RAVLT-long delay	-0.21 (1.14)	0.49 (3.35)	11.76	20	0.94*
9HPT-dominant**	-	-1.71 (1.99)	-	45	-
9HPT-nondominant**	-	-1.59 (1.84)	-	50	-

Note: SDMT = Symbol Digit Modalities Test; RAVLT = Rey Auditory Verbal Learning Test; 9HPT = 9 Hole Peg Test. All measures are reported as z-scores. *Mann-Whitney U tests were used to compare groups. All other data are analyzed using independent t-tests. Data are reported as mean and standard deviation. **Indicates that data is only available for 19 patients. [†] Indicates the measures used in the criterion for defining cognitive impairment, i.e. 2 of 8 failed tests. WASI-Full-2-IQ is comprised of two subtests: Vocabulary and Matrix Reasoning.

Behavioural data on the Go/No-go task (Objective 1) and the influence of age at disease onset and cerebral tissue damage on Go/No-go performance parameters (Objective 2).

Table 6 summarizes the behavioural performance on the Go/No-go task for the controls and patients. All participants scored above the minimum 75% accuracy rate on the Go/No-go task. Groups did not differ with respect to RT and accuracy on the Go/No-go. Accuracy ranged from 92% to 100% for controls and 91% to 99% for patients. Although mean RT was slightly longer for patients than controls, the difference was not significant. Likewise, there was no difference in number of commission and omission errors. The total number of commission errors made by controls ranged from 1-15 (median score = 9) and the total number of commission errors made by patients ranged from 2-16 (median score = 4.5). The total number of omission errors made by controls ranged from 0-7 (median score = 0) and by patients ranged from 0-14 (median score = 0). In order to examine the possibility of increased variability in RT over the duration of the task (which may occur due to increased fatigue over the task), a repeated measures ANOVA was used to compare RT on Block 1 to Block 2 in patients and controls. Results revealed no main effect of block ($F(1, 1) = 0.32, p = 0.57$) or an interaction between block and group ($F(1, 1) = 0.33, p = 0.57$).

Table 6

Behavioural data for Go/No-go task

Measure	<u>Healthy Controls</u>	<u>Patients</u>	<u>Group difference</u>	
	n=17	n=20	<i>p</i>	Partial η^2
Reaction Time (ms)	333.70 (41.04)	358.85 (54.42)	0.13	0.065
Accuracy (% correct)	96.48 (2.08)	96.61 (2.67)	0.87	0.001
Commission Errors*	9 (1-15)	4.5 (2-16)	0.39	0.021
Omission Errors*	0 (0-7)	0 (0-14)	0.35	0.026

Note. Reaction time was only reported for correct responses greater than 200 ms; Data reported as mean and standard deviation except where indicated. *Mann-Whitney tests were used and median scores and ranges are reported.

Table 7 and 8 show the correlations between the Go/No-go behavioural outcomes and demographic, clinical, and MRI correlates for patients and controls. Age at evaluation did not correlate with performance parameters, nor did measures of fatigue, depression symptoms, and fine motor dexterity on the 9HPT. Regarding clinical variables, younger age at disease onset (controlling for disease duration) was associated with lower accuracy ($r = 0.38$), and this difference approached significance (p (one-tailed) = 0.054) (See Figure 3). Closer examination of this relationship revealed that patients with younger disease onset made more commission errors. Age at disease onset was not associated with reaction time ($r = 0.31$, p (one-tailed) = 0.10).

Regarding MRI correlates, patients did not show a significant relationship between normalized brain volume and thalamic volume with accuracy or reaction time on the Go/No-go task. Regarding lesion volume in the patient group, poorer performance on the GNG task approached significance with higher T1-weighted lesion volume ($r = -0.32$, $p = 0.09$). Regarding the control group, poorer reaction time on the GNG task was significantly correlated with lower thalamic volume ($r = -0.702$, $p = 0.001$).

In summary, controls and patients performed similarly on the Go/No-go task in terms of all behavioural measures. Age at evaluation, fatigue, depression symptoms, and fine motor dexterity on the 9HPT did not correlate with performance parameters. Younger age at disease onset (controlling for disease duration) was associated with lower accuracy (at a trend level), revealing that patients with younger disease onset made more commission errors as compared with patients who were older at time of disease onset. Higher T1-weighted lesion volume was also marginally associated with lower accuracy. Longer reaction time associated with lower thalamic volume in the control group, but not the patient group (See Figure 4).

Table 7

Correlations Between Go/No-go Behavioural Outcomes and Clinical-Demographic and MRI Outcomes for the MS Group

Variable	Go/No-go Outcome	
	RT	Accuracy
Age at assessment	0.37	0.33
Age at disease onset [†]	0.31	0.38
Duration of disease	0.34	0.13
PedsQL Total Fatigue Score*	0.17	0.11
CES-D Depression Total Score*	0.20	0.18
9 Hold Peg Test (9HPT)-Dominant hand* (z-score)	-0.14	-0.05
Normalized Brain volume	0.062	0.096
Thalamic brain volume	-0.098	0.243
Log T2-weighted LV	0.03	-0.23
Log T1-weighted LV	0.25	-0.32

Note. Pearson correlations used (one-tailed), except where a * is indicated for which Spearman's correlation was used. [†] Controlling for disease duration. Bolded values indicate $p < 0.10$.

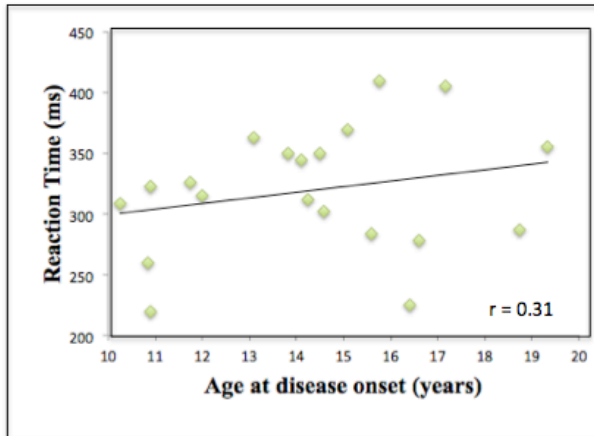
Table 8

Correlations Between Go/No-go Behavioural Outcomes and Clinical-Demographic and MRI Outcomes for the Healthy Controls

<i>Variable</i>	<i>Go/No-go Outcome</i>	
	RT	Accuracy
Age at assessment	-0.41	-0.14
PedsQL Total Fatigue Score*	-0.002	-0.03
CES-D Depression Total Score*	0.10	-0.09
9 Hold Peg Test (9HPT)-Dominant hand* (z-score)	0.36	0.1
Normalized Brain volume	-0.096	0.29
Thalamic volume	-0.702	0.079

Note. * Indicates Spearman's correlation one-tailed test used ($p < 0.05$). If not indicated Pearson correlation one-tailed test used. Bolded values indicate $p < 0.05$

A. Reaction Time



B. Accuracy

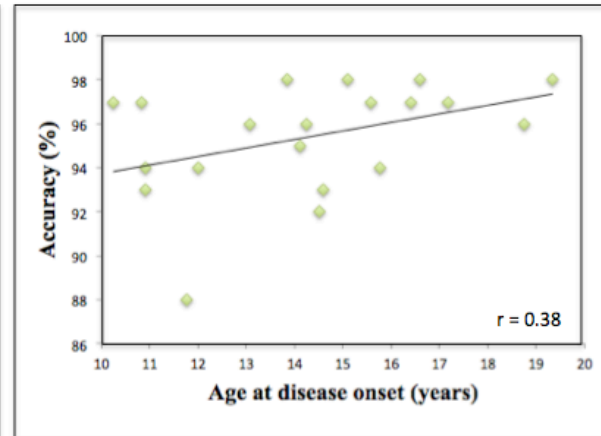
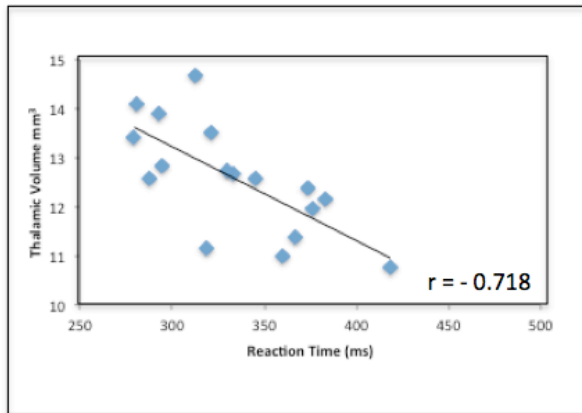


Figure 3. A. Correlation between reaction time and age at disease onset (controlling for disease duration) for MS group. B. Correlation between accuracy and age at disease onset (controlling for disease duration) for MS group.

A. Controls



B. MS group

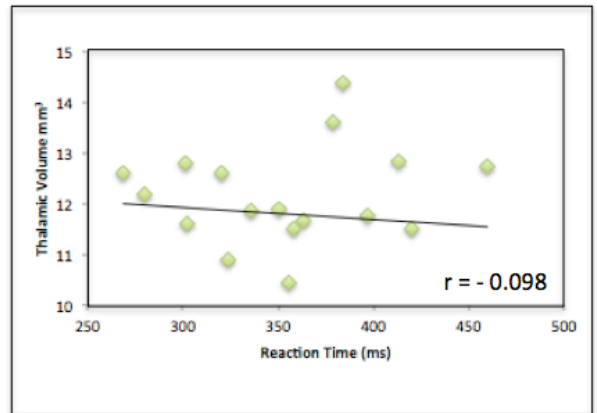


Figure 4. A. Correlation between reaction time and thalamic volume for controls. B. Correlation between reaction time and thalamic for patients.

Functional MRI data analysis of the No-go stimuli (Objective 3)

Activation patterns were reported for each group separately and then were compared to one another. Only significant activation patterns were identified using a cluster threshold of $Z > 2.3$ ($p < 0.05$). As shown in Figure 5, healthy controls showed significant activation in diffuse brain regions, including (1) bilaterally in the anterior cingulate gyrus, cerebellum, frontal lobe, inferior frontal gyrus, medial frontal gyrus, superior frontal gyrus, posterior cingulate gyrus, bilateral parietal lobe (2) right hemisphere: precuneus, temporal lobe; and in the (3) left hemisphere: inferior occipital gyrus, occipital lobe, superior temporal lobe (Table 95). The same contrast in patients showed a less extensive pattern of threshold activation. As shown in Figure 6, patients showed significant activation in the (1) right hemisphere: precuneus, middle frontal gyrus, parietal lobe and superior frontal gyrus; and (2) left hemisphere: middle temporal and inferior temporal gyrus, and fusiform gyrus (Table 10). When patients and controls were examined for between group differences, healthy controls showed more activation than patients in the following regions: (1) bilaterally in the cerebellum and precentral gyrus; (2) the right hemisphere: precuneus and lateral occipital cortex; (3) left hemisphere: brainstem, superior frontal gyrus and parahippocampal gyrus (Table 11, Figure 7). Patients did not show more activation than controls in any region.

In summary, controls exhibited more extensive brain activation patterns than patients in response to the No-go stimulus on the GNG task (Table 12). Surprisingly, posterior regions of the brain (cerebellum, precuneus, occipital cortex, brainstem) as well as the superior frontal gyrus and the parahippocampal gyrus were recruited to a greater extent in the controls compared with the patient group.

Table 9

Regions of interest activated by controls during No-go trials

Region/gyrus	Hem.	Talairach Coordinates			Z	Cluster Size (Voxels)
		x	y	z		
Frontal Lobe	R	13	36	-4	2.57	77
Frontal Lobe	L	-45	48	-3	3.04	38
Superior Frontal Gyrus	R	19	22	48	3.64	1333
Superior Frontal Gyrus	L	-24	34	48	3.03	25
Inferior Frontal Gyrus	R	58	10	27	3.04	58
Inferior Frontal Gyrus	L	-52	19	16	4.18	8792
Medial Frontal Gyrus	R	10	49	37	3.63	2314
Medial Frontal Gyrus	L	-15	58	-4	3.10	312
Middle Frontal Gyrus	R	44	16	45	4.16	1851
Parietal Lobe/Cingulate Gyrus	R	4	-40	33	4.78	60848
Superior Parietal Lobe	L	6	-71	50	2.50	1
Precuneus	R	14	-55	53	2.54	50
Posterior Cingulate Gyrus	R	45	-16	49	3.65	5507
Anterior Cingulate	R	8	57	-9	3.59	449
Anterior Cingulate	L	-11	34	-10	3.11	432
Middle Temporal Gyrus	L	-54	-55	-8	4.20	8424
Temporal Lobe	R	47	-10	-18	4.26	3895
Occipital Lobe	L	-4	-85	38	3.05	14
Inferior Occipital Gyrus	L	-30	-90	-12	2.52	55
Posterior Cerebellum	L	-53	-58	-20	3.03	31

Cerebellum	R	16	-74	-28	4.23	5853
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Note. L=Left, R=Right. Volume per voxel $2.997 \times 2.997 \times 4=35.93\text{mm}^3$. x,y,z are peak of mass coordinates for each cluster. Significant activation ($p<0.05$, $Z > 2.5$ Threshold Cluster)

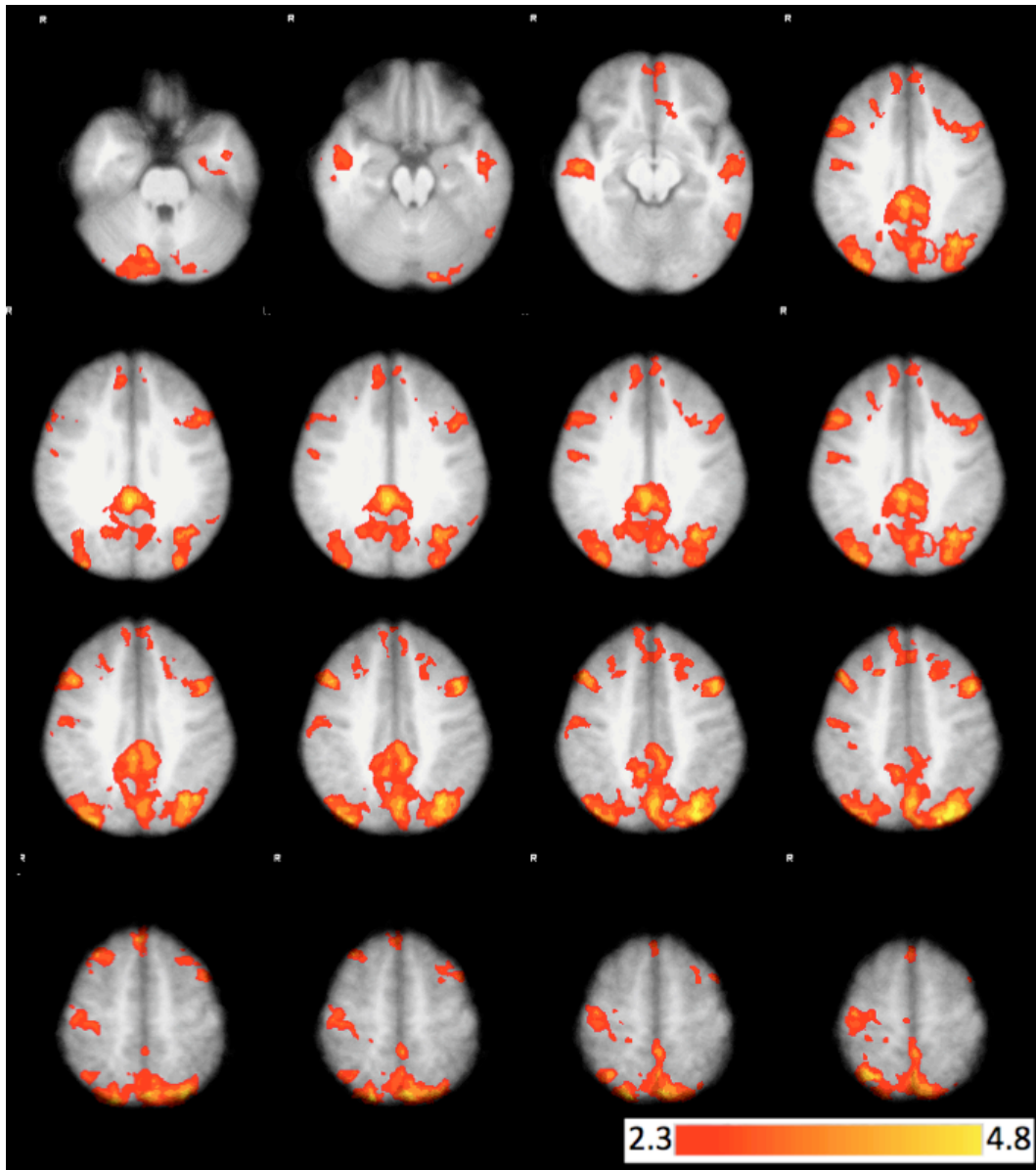


Figure 5. Brain regions showing significant activation ($p < 0.05$, $Z > 2.3$ Threshold Cluster) to No-go stimuli for controls. Axial slices are in radiological convention (left hemisphere is on the right). The bar on the right indicates activations based on z-score.

Table 10

Regions of interest activated by MS patients during No-go trials

Region/gyrus	Hem.	Talairach Coordinates			Z	Cluster Size (Voxel Size)
		x	y	z		
Superior Frontal Gyrus	R	44	21	50	2.99	21
Middle Frontal Gyrus	R	46	28	26	4.18	6904
Precuneus	R	12	-48	39	4.77	11138
Parietal Lobe	R	41	-65	36	4.79	5496
Middle Temporal Gyrus	L	-37	-73	30	4.77	4457
Interior Temporal Gyrus	L	-64	-51	-7	3.03	24
Fusiform Gyrus	L	-48	-55	-19	2.5	2

Note. B=Bilateral. L=Left, R=Right. Volume per voxel $2.997 \times 2.997 \times 4=35.93\text{mm}^3$. x,y,z are peak of mass coordinates for each cluster. Significant activation ($p<0.05$, $Z > 2.3$ Threshold Cluster)

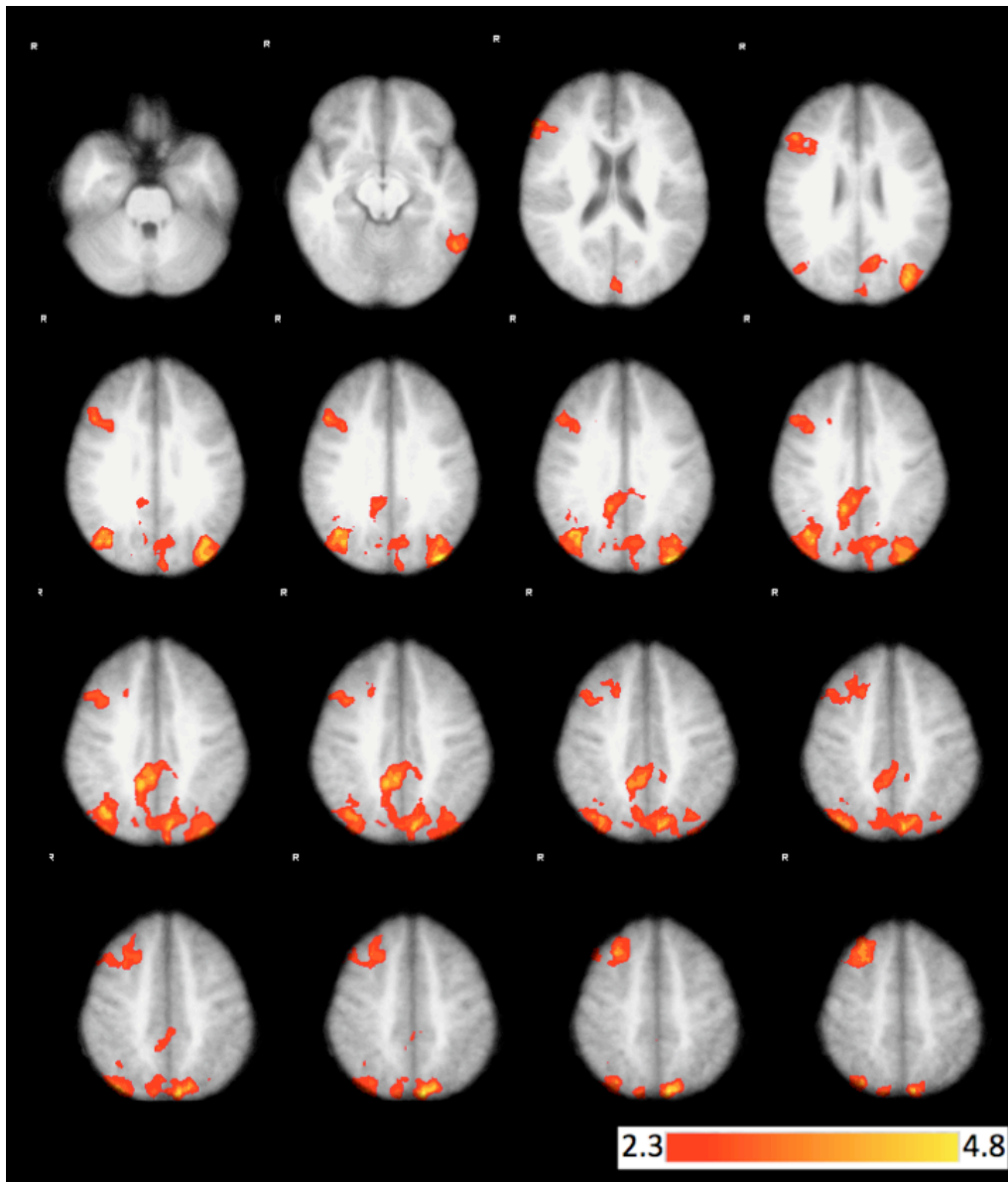


Figure 6. Brain regions showing significant activation ($p < 0.05$, $Z > 2.3$ Threshold Cluster) to No-go stimuli for pediatric-onset MS patients. Axial slices are in radiological convention (left hemisphere is on the right)

Table 11

Regions showing greater cerebral activation by controls compared to patients during No-go

Trials

Region/gyrus	Hem.	Talairach Coordinates			Z	Cluster size (Voxels)
		x	y	z		
Superior Frontal Gyrus	L	-22	-8	74	4.10	667
Precentral Gyrus/SMA	R	4	-16	72	3.58	534
Precentral Gyrus	L	-35	-13	70	2.99	38
Superior Parietal Lobe	R	33	-48	64	2.50	1
Precuneus	R	13	-58	58	3.07	354
Parahippocampal Gyrus	L	-27	-27	-27	3.05	7
Lateral Occipital Cortex	R	27	-65	66	3.48	401
Posterior Cerebellum	L	1	-63	-5	2.50	1
Cerebellum	R	18	-55	-29	3.13	8382
Brainstem-midbrain	L	-14	-20	-11	3.70	4504

Note. B=both. L=Left, R=Right. Volume per voxel $2.997 \times 2.997 \times 4=35.93\text{mm}^3$. x,y,z are centre of mass. MS=patients with MS, Con= controls. Significant activation ($p<0.05$, $Z > 2.3$ Threshold Cluster).

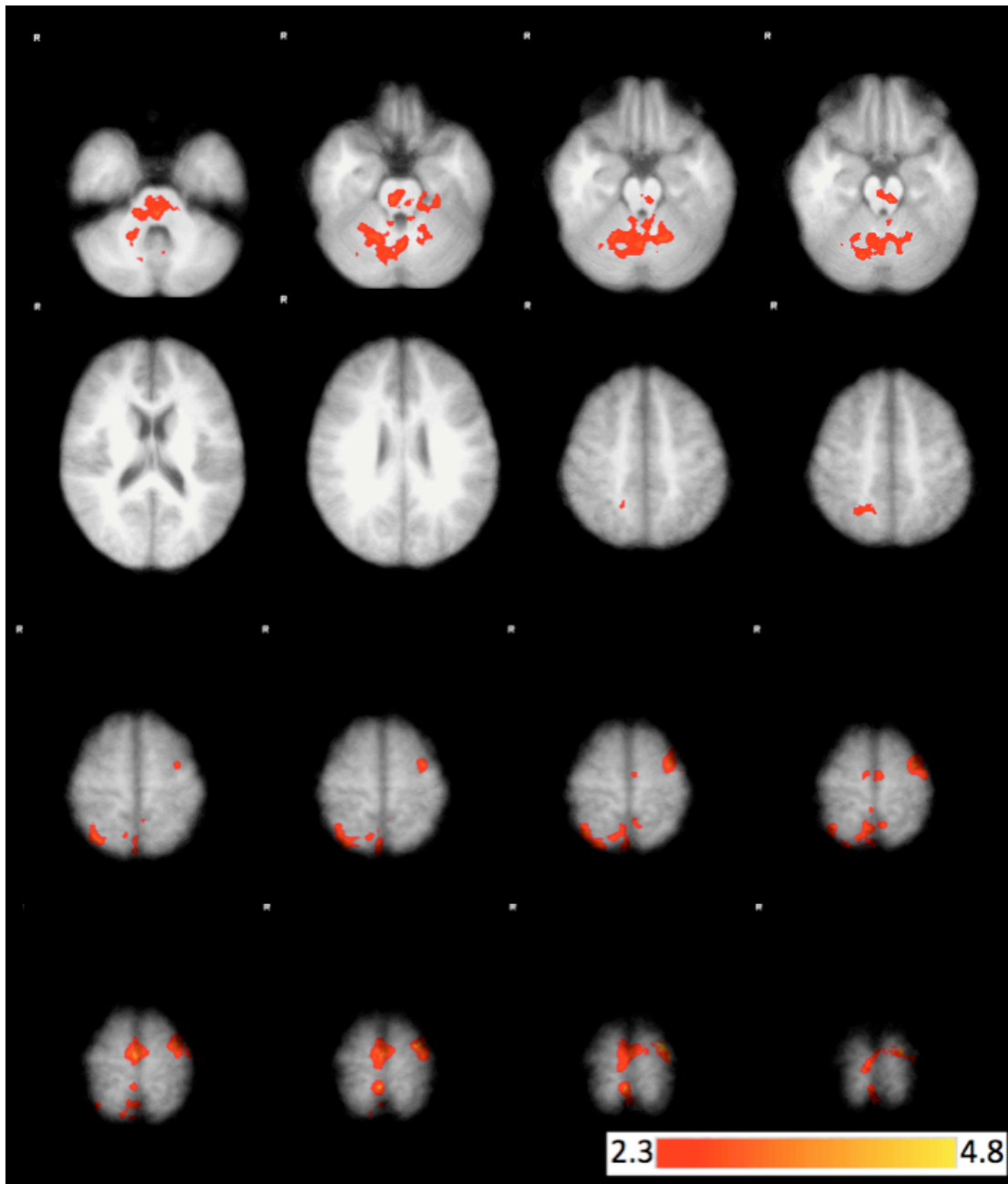


Figure 7. Brain regions showing significant response ($p < 0.05$, $Z > 2.3$ Threshold Cluster) to No-go stimuli for Controls compared to patients. Patients did not show greater significant activations patterns than controls. Axial slices are in radiological convention (left hemisphere is on the right).

Table 12

Between group differences in brain activation patterns between patients and controls.

Brain Region	Hem.	Controls	MS	Controls>MS
Frontal Lobe	Bil.	X		
Superior Frontal Gyrus	L	X		
Superior Frontal Gyrus	R	X	X	X
Inferior Frontal Gyrus	Bil.	X		
Medial Frontal Gyrus	Bil.	X		
Middle Frontal Gyrus	R	X	X	
Precentral Gyrus	Bil.			X
Parietal Lobe	R	X	X	
Superior Parietal Lobe	L	X		X
Precuneus	R	X	X	X
Posterior Cingulate Gyrus	Bil.	X		
Anterior Cingulate Gyrus	Bil.	X		
Parahippocampal	L			X
Fusiform	R		X	
Temporal Lobe	R	X		
Inferior Temporal Gyrus	L		X	

Middle Temporal Gyrus	L	X	X	
Occipital Lobe	L	X		
Inferior Occipital Gyrus	L	X		
Lateral Occipital cortex	R			X
Cerebellum	R	X		X
posterior cerebellum	L	X		
Brainstem-midbrain	L	X		

Discussion

The present investigation had three aims. First, the simple Go/No-go task was used to examine response inhibition in patients with pediatric-onset MS and age-and-sex matched controls. As with previous neuropsychological literature (Till et al., 2012), cognitively intact pediatric-onset patients with MS were not expected to demonstrate difficulties with performance on the task because response inhibition is rarely compromised in comparison to other executive functioning tasks. Second, the Go/No-go performance parameters were used to evaluate the association of age at disease onset and cerebral tissue damage. Literature shows that attentional control and response inhibition networks develop throughout childhood, which places patients with a younger age at disease onset at risk of poorer performance on a task of response inhibition. Likewise, the literature reports that higher levels of cerebral tissue damage (as indicated using structural MRI) predict poorer performance on the simple Go/No-go task. The final aim was to examine the pattern of cerebral activation produced by childhood-onset MS patients compared to healthy controls. Studies conducted in adults with MS (Bonnet et al., 2010) as well as adolescents with MS (Rocca et al., 2003) show recruitment of supplementary cerebral areas, in addition to expected brain regions, in order to perform as well as healthy controls.

In the present study, two main findings are reported: (1) pediatric-onset MS patients who are cognitively intact perform equally well as controls on a simple task of response inhibition (Go/No-go); and, contrary to our hypothesis, (2) a less extensive brain activation is demonstrated by pediatric-onset MS patients when performing a task requiring response inhibition as compared with the age-matched controls. While none of the clinical and MRI variables correlated significantly with Go/No-go task performance in the patient sample, two interesting relationships emerged that were consistent with the hypothesis and therefore warrant further discussion. First, better performance on the Go/No-go task was associated at a trend

level ($p = 0.054$) with older age at disease onset, supporting an early vulnerability perspective. Second, higher lesion volume was associated with lower accuracy, again at a level that approached significance ($p < 0.10$). These findings will be discussed in more detail below.

Objective 1: To examine response inhibition in patients and age-matched controls using a simple Go/No-go task

As hypothesized, cognitively intact pediatric-onset patients did not demonstrate significant deficits on the simple Go/No-go task with respect to accuracy and reaction time. This finding was expected given the clinico-demographic characteristics of the patient group evaluated in the current study. Specifically, in terms of demographic features, both patients and controls were similar in terms of age, education, and social economic status, thus ruling out the possibility of better performance on the GNG task due to maturational or socio-demographic differences. In terms of clinical features, both groups were similar in terms of mood as assessed by the CES-D, and fatigue symptoms as measured by Varni PedsQL (general fatigue, cognitive and sleep/rest scales). This is important because both depression and fatigue may reduce speed of processing (Diamond, Johnson, Kaufman, & Graves, 2008), which in turn, would have influenced performance on the GNG task. Elevated depression and physical fatigue scores have been found to mediate the strength of the relationship between processing speed and cognitive tasks that require learning and memory. Moreover, the possibility that the patients showed ‘increased fatigue’ over the length of the GNG task was ruled out by examining changes in RT that occurred between block 1 and block 2 of the task. Results showed that both patients and controls performed similarly (measured by RT and accuracy) across the two blocks. This suggests that patients maintained their RT over the length of the relatively simple GNG task.

Most importantly, the MS group performed similarly to controls across all cognitive tests. Both groups were very similar to one another cognitively, even with respect to the number of participants meeting criteria for cognitive impairment in each group. This is important because it permitted a comparison of the functional activations in the brain regions using a well-matched control group. Previous literature (Loitfelder et al., 2011) has shown that cognitively impaired patients show different patterns of activation and thus the results to objective 3 would be much different if the group was a more heterogeneous sample that included more patients with cognitive impairment.

In comparison to previous studies that report cognitive impairment in pediatric-onset MS patients (Amato et al., 2008; Banwell & Anderson, 2005; MacAllister et al., 2005; Till et al., 2011), our sample of patients performed similarly to controls and showed minimal deficits on the cognitive screening battery. Thus, there was no reason to suspect that the patient group would have difficulty on the simple Go/No-go task in terms of accuracy and reaction time. In contrast, if the Go/No-go task used a more complex version, as done in previous studies (Bonnet et al., 2010), a significant difference between patients and controls would be expected to occur with respect to both performance parameters (reaction time), as well as cerebral activations. With higher cognitive demands (as seen in the complex Go/No-go condition), there is an increased cognitive load and recruitment of extra regions that become saturated in patients with MS. Despite greater activation, patients perform worse than controls (Bonnet et al., 2010). In the case where patients and controls performed differently on the task from one another, it would be difficult to conclude whether the supplementary areas aided performance.

Despite reduced fine motor dexterity (as indicated by a low mean score on the 9 Hole Peg Test (9HPT)), patients did not show slower reaction time on the Go/No-go task. The lack of association between the 9HPT and the functional MRI task ($r = -0.14$) may be explained by the

fact that the simple button response for the Go/No-go task does not require fine motor dexterity (*i.e.* it is not as complex a motor movement as picking up a small peg and placing it into a hole quickly).

In summary, performance was similar for controls and patients across cognitive tasks, with two patients and two controls classified as cognitively impaired. Likewise, performance on the Go/No-go task was similar for both groups and consistent with the previous adult MS literature demonstrating intact inhibitory control using similar Go/No-go paradigms (e.g. Bonnet et al., 2010; Smith et al., 2009).

Objective 2. To evaluate the influence of age at disease onset and cerebral tissue damage on Go/No-go performance parameters

It was hypothesized that younger age at disease onset would result in worse performance on the Go/No-go task. Results of the current study showed a trend between younger disease onset (controlling for duration of disease) and lower accuracy ($r = 0.38, p = 0.054$). Inspection of the types of errors made by patients indicated that commission errors were more common in the young disease onset patients. This finding was irrespective of age, as age at evaluation did not show a correlation with performance parameters. The current findings are consistent with those reported by Till et al. (2012) showing a significant association between younger age at onset and inhibitory control as assessed using the Colour-Word Interference tests on the Delis-Kaplan Executive Function Scale (DKEFS). Other studies in pediatric-onset MS (Banwell & Anderson, 2005; MacAllister et al., 2005) have also related younger age at disease onset with difficulties on tasks that require self-generated organizational strategies, efficient processing speed or working memory, all of which are executive functions. The findings are also concordant with prior research conducted in children with traumatic brain injury showing that both pre-injury ability

and age at injury are both significant predictors of executive functioning skills (Anderson & Catroppa, 2005; Anderson et al., 2008). Taken together, these findings emphasize age at disease onset as a predictor of executive dysfunction and implicate the vulnerability of immature neural networks.

The present results suggest a greater vulnerability of the immature brain and refute the Kennard principle which states that the immature brain is more plastic and less vulnerable to insult than a mature brain (Montour-Proulx et al., 2004). A study (Duval et al., 2008) examining the relationship between time of brain insult and IQ outcomes in 725 patients who ranged in age from 0 to 84 years found that those who suffered the brain insult in childhood had lower IQ scores and a deterioration in IQ over time whereas the adult-onset group's IQ did not show deterioration. These results highlight the vulnerability of the immature brain. In another study, Crowe, Catroppa, Babl and Anderson (2013) examined inhibitory control, attentional control and information processing in three to six year old children who sustained a mild to moderate-severe traumatic brain injury (TBI) before 3 years of age compared to healthy age-matched controls. On a task of inhibitory control (NEPSY-II Statue subtest), children who had a TBI prior to age 3 performed significantly worse than healthy children. Inhibitory control begins to develop prior to this age therefore it is not surprising that insult would interfere with proper development of inhibitory control. The study found no difference in performance on tasks of auditory attention (examining selective attention and vigilance) and information processing (examined using WPPSI-III Coding subtest) between the two groups (Crowe et al., 2013). Decreases in attention and information processing may not have been seen since both of these executive functioning skills continue to develop after age 6 and may only become apparent deficits over time as environmental demands increase (Crowe et al., 2013).

After children sustain a brain injury they must not only recover the affected functions but they must also acquire new skills. The rate of acquiring new skills in these children, however, may be restricted by of the brain insult, causing children to fall even more behind same-aged peers (Duval et al., 2008). Cognitive impairment was examined at two time points, 3 months and 30 months after insult (Anderson et al, 2005). At 3 months after injury, children who experienced insult between birth and 12 years of age had similar levels of impairment. However, when these same children were examined at 30 months post insult, children who acquired insult prior to age 7 had a slower recovery and performed worse than children who acquired insult later (12 years of age). These findings suggest that deficits acquired earlier may become more pronounced with time and may emerge as a result of increased environmental demands (Anderson et al. 2005).

Inhibitory control appears to be one of the first executive functions to develop and mature as reflected through age-dependent change in brain activations required to effectively exhibit inhibitory control. In an fMRI study (Marsh et al., 2006), the Stroop interference task was used to examine inhibitory control in 70 healthy individuals between the ages of 7 to 57 years of age. Results revealed a positive relationship between activation of the right inferolateral prefrontal cortex (BA44/45) and right lenticular nucleus with age. Greater activity in the right inferolateral prefrontal cortex was also accompanied by better inhibitory control, as measured by accuracy rate (Marsh et al., 2006). There was also deactivation in the mesial prefrontal cortex (BA10), subgenual anterior cingulate cortex (BA 24), and posterior cingulate cortex (BA 31) with increased age, which corresponded with a decrease in task difficulty in older subjects (Marsh et al., 2006). Insults that occur during critical periods of executive function development may result in abnormal development of neural networks that underlie these executive skills.

The extent of brain injury severity and location of brain insult (Duval et al., 2008; Crowe, Catroppa, Babl, & Anderson, 2013) also plays an important role in predicting degree of

impairment. In the present study, it was hypothesized that higher cerebral tissue damage, as assessed by lesion volume and volume of the entire brain and thalamus, will contribute to worse performance on the Go/No-go task. Results showed that lesion volume was not correlated with reaction time on the Go/No-go task. However, T2-weighted lesion volume and T1-weighted lesion volume both showed a negative association with accuracy ($p = 0.08$ and $p = 0.098$, respectively). The observed weak relationship between lesion volume and reaction time is consistent with prior studies showing a weak relationship between lesion volume and cognitive dysfunction (Benedict et al., 2004; Till et al., 2011; Till et al., 2012). These findings suggest that lesion volume may not be sensitive enough to the subtle changes that occur in the brain that could be responsible for cognitive impairment (Rovaris et al., 1998, Rovaris et al, 2006). There are several reasons why the relationship between lesion volume and RT was not seen: First, the lesions may not exert strong influence on simple reaction time (for example, reaction time may be more dependent upon white matter integrity); Second, the “lesion volume” metric does not provide information regarding the spatial topography of the lesions (i.e. unclear whether the lesions consist of a number of small lesions throughout the brain or a large lesion) (Rovaris et al., 1998; Rovaris et al, 2006). Third, the overall lesion volume was quite low in the current sample of patients relative to other samples of MS patients.

In the current study, patients exhibited lower normalized brain volume compared to controls ($p = 0.003$), and lower thalamic volume compared to controls, with the difference approaching significance ($p < 0.06$). Brain volume represents the overall health of the brain. Patients with pediatric-onset MS exhibit reduced normalized brain volumes suggesting an overall failure of the brain to develop at a rate that is age appropriate (Kerbrat et al., 2012; Till et al., 2011). Volume loss in the thalamus can occur before observable volume loss in the entire brain (Kerbrat et al., 2012; Mesaros et al., 2008). Measures detecting changes in individual subcortical

grey matter structures are more sensitive than measuring whole brain volume changes. The thalamus plays an important role in cognition as a result of its extensive circuitry connecting multiple brain regions that influence global cognitive functioning, attention, arousal, memory, mental processing speed, visuomotor integration, and expressive vocabulary (Blinkenberg et al., 2000; Houtchens et al., 2007; Till et al., 2011; Van Der Werf et al., 2001). Our results are similar to Till et al., (2011) who found a significant difference in both normalized brain volume and thalamic volume between pediatric-onset patients with MS and healthy controls, with patients exhibiting lower thalamic and normalized brain volume.

Objective 3. To examine whether cognitively intact childhood-onset MS patients produce a less efficient pattern of cerebral activation compared with age-matched healthy controls

It was hypothesized that pediatric-onset MS patients would recruit supplementary cerebral areas, in addition to expected brain regions, when performing a simple Go/No-go task, compared to healthy controls. In the present study controls showed the expected pattern of activation whereas patients did not (Simmonds et al., 2008; Bonnet et al., 2010) however some differences did exist. Counter to our hypothesis, a more extensive pattern of brain activation was noted in controls as compared with the patient group in response to the No-go stimulus.

Previous literature in healthy controls has identified the inferior occipital gyrus, fusiform gyrus/posterior cerebellum, pre-SMA and precuneus as regions that are activated during the response inhibition component of the simple Go/No-go task (Simmonds et al., 2008). In patients with MS, the cingulate gyrus, cerebellum, temporo-occipital region, temporal gyrus and medial frontal gyrus have been identified as regions involved in inhibitory control (Bonnet et al., 2010).

When activation patterns were examined within groups, controls showed regions of activation that were similar to previous literature, but also recruited additional brain regions.

Amongst controls relative to patients, activations were more prominent in the occipital region (versus an absence of activation in this entire region in the patients), parietal lobe (including the precuneus and superior parietal lobe), frontal regions (superior frontal gyrus and the precentral gyrus/SMA), and posterior regions of the brain (including the cerebellum and brainstem/midbrain). Controls also showed activation patterns similar to those identified in previous literature for patients with MS (Bonnet et al., 2010), including the cingulate gyrus with bilateral activation, right cerebellum, right lateral occipital cortex, right temporal lobe and left temporal gyrus, and bilaterally in the medial frontal gyrus (see *table 2*). Unlike previous literature, controls showed activation bilaterally in the parietal lobe and left superior parietal lobe.

When patients were examined as a group they showed activation in the right precuneus and left fusiform gyrus, as stated in literature on healthy controls (Simmonds et al., 2008) and additionally in the right superior and middle frontal gyri, right parietal lobe and left inferior and middle temporal gyri. Unlike previous literature on patients with MS (Bonnet et al., 2010), patients did not show activation in the right cingulate gyrus, right temporo-occipital lobe, right temporal gyrus or the medial frontal gyrus.

When the two groups were compared, controls showed stronger activation in the right superior frontal gyrus, left superior parietal lobe, precuneus, right cerebellum, precentral gyrus (bilaterally), left parahippocampal gyrus, right lateral occipital cortex, and left brainstem.

The simple Go/No-go task can be separated into two components: visual perception and response execution. These two components each have specific brain regions that are required to perform the task well. In terms of visual perception, the inferior occipital gyrus, temporal gyrus, and fusiform gyrus each play an important role in stimulus recognition. The occipital gyrus plays an important role in vision, particularly with respect to colour, and pattern, with an important

role in stimulus recognition (Barrett et al., 2001; Wang et al., 2013). In addition, the temporal gyrus is involved in higher order vision, such as visual control of actions with recognition and object identification occurring in the inferotemporal cortex and projecting to the posterior parietal region in order to mediate the required sensorimotor actions toward an object (Betts & Wilson, 2010; Goodale & Milner, 1992). The temporal and occipital gyri are interconnected, and communicate information to one another during stimuli recognition, particularly with whole face stimuli, but also with facial features and head outlines (Betts & Wilson, 2010). The fusiform gyrus located in the temporal lobe is also a visual association area that is connected with the posterior parietal and prefrontal areas (Bullier, Schall, & Morel, 1996; Sporns, 2011). Activation in the fusiform gyrus is associated with correctly classifying a cue. Feedback from higher order regions is then used to recognize the cue, which in turn projects the information forward in order to inhibit the pre-potent response (Simmonds et al. 2008). In the present study, both groups showed activation in the fusiform/posterior cerebellum, temporal gyrus, with controls showing activation in the occipital gyrus and parietal lobe and prefrontal activation.

In terms of response execution, the cingulate gyrus, precuneus, pre-SMA, cerebellum and medial frontal gyrus all play an important role during the Go/No-go task. The posterior and anterior cingulate gyrus make up part of the attentional system and are thought to play roles both in attention and motivation (Rubia, Smith, Brammer, Toone, & Taylor, 2005). Specifically activity in the posterior cingulate gyrus is associated with unsuccessful inhibition whereas activity in the anterior cingulate gyrus is associated with successful inhibition. Previous literature on Attention Deficit Hyperactivity Disorder (ADHD) has pointed to the idea that reduced activation in the posterior cingulate reflects an inability to appropriately attend to stimuli after making errors (Rubia et al., 2005). The role of the anterior cingulate cortex has also been implicated in reward processing, performance monitoring, execution of control, and action

selection (Shenhav, Botvinick, & Cohen, 2013). The anterior cingulate gyrus uses performance monitoring to decide the amount of control needed to execute an action (Shenhav et al., 2013). The precuneus is involved in movement initiation and control (Rocca et al., 2005), and, with its connections to the medial prefrontal cortex and inferior parietal cortex, plays a partnering role in order to promote efficient information flow and to enable higher intellectual performance (Sporns, 2011). In the present study, only controls showed activation in the cingulate gyri suggesting more attention spent on monitoring performance. Both controls and patients showed activation of the precuneus, parietal lobe, superior and middle frontal gyri, which all play a partnering role in enabling higher intellectual performance; however, only controls activated the entire frontal lobe and medial frontal gyri. Although behaviorally there was no significant difference in performance on the Go/No-go task, perhaps if the stimuli were more difficult to discern and a greater need for monitoring stimuli was required, the controls would perform better than patients given that these areas are already activated.

The pre-SMA is connected to prefrontal regions, the primary motor regions and the spinal cord (Picard & Strick, 2001). These connections suggest the pre-SMA plays a role in the ability to switch from the execution of a response (which is automatic) to the withholding of a response by listening to feedback from higher order areas like the prefrontal regions (Simmonds et al., 2008). Frontal lobe lesion studies have documented an association between poor response inhibition and lesions in the superior medial frontal lobe, suggesting that the medial frontal lobe plays a role in not only inhibiting a response but also rapidly inhibiting that response (Floden & Stuss, 2006; Picton et al., 2006). The medial frontal gyrus is important in decision-making, as indicated by a study examining gambling behaviours in patients with bilateral lesions to the ventromedial prefrontal cortex (Bechara, Tranel, & Damasio, 2000). These patients had difficulty in decision-making throughout the task, and also demonstrated a lack of sensitivity to

consequences. In the present study, only controls activated the frontal lobes, superior, inferior, middle and medial frontal gyri, and precentral gyrus; the patients only showed activation in the right superior and middle frontal gyri. In Bonnet et al., (2010), better performance on the Go/No-go by patients with MS was correlated with greater activation of the medial frontal gyrus. A difference between our patients and those in Bonnet et al. (2010) may be that their patients were diagnosed with MS in adulthood where their frontal lobes and connections were fully established whereas in our patient group the disease onset occurred prior to adulthood and thus the younger patients may be less able to recruit frontal regions because they were not developed normally. Moreover, in the comparison study, average disease duration was shorter than in the present study (1.4 ± 2.5 versus 5.07 ± 3.10 years), which may also contribute to differences in activation patterns between the studies.

In the present study, only controls showed activation in the cerebellum and brainstem. The brainstem is important in many physiological functions (cardiac output, controlling blood pressure, respiration, sleep/wake cycle) thereby it is possible that the activation pattern observed in controls may have also resulted from physiological sources of noise (lying close to major arteries and CSF spaces) which may have generated time varying signals (Brooks, Faull, Pattinson, & Jenkinson, 2013), however this does not explain why we did not observe the same pattern in patients. Research has also pointed to the involvement of the brainstem when imagining a movement, such as when a person imagines performing a motor action (La Fourgère et al., 2010). This activation may have been observed in controls as they imagined their actions to the stimuli, which may have been part of their monitoring of their own actions.

The cerebellum is important in motor preparation and response inhibition, with increased cerebellar activity associated with increased frontal lobe activity as task demands increase (Smith et al., 2009). The cerebellum also plays an important role in the execution of voluntary

movement, even when movement is inhibited (Mostofsky et al., 2003). An fMRI study examining motor control in patients with MS (Saini et al., 2004) found that patients displayed significant connectivity between the left premotor neocortex and the ipsilateral cerebellum. The authors suggested that these changes in functional connectivity in the patient group reflect adaptive changes in the brain following brain insult and serve the purpose of aiding the patient in his ability to sustain motor control (Saini et al., 2004).

In recent years, the importance of the cerebellum has been highlighted in a variety of cognitive processes, including language, visual-spatial, executive control and working memory processes, but the precise role of the cerebellum in these cognitive processes still requires further investigation (Stoodley, 2012). The role of the cerebellum in motor tasks includes preparation and execution of movements (Cui et al., 2000) and previous literature in patients with MS has shown increased connectivity and bilateral cerebellar activity, consistent with adaptive changes to brain insult (Saini et al., 2004). However, other studies conducted in MS show decreased activation or connectivity of this brain structure, consistent with the current results showing a lack of activation in the cerebellum.

Recent work has been examining the structure and function of the cerebellum in MS patients to understand its role better. In one study that used DTI to examine white matter integrity, adult MS patients who were cognitively impaired were shown to have reduced white matter integrity in cortical brain areas, thalamus, uncinate fasciculus, brainstem and cerebellum (Hulst et al., 2013). Likewise, in patients with pediatric-onset MS, cognitive impairment was associated with gray matter and white matter atrophy in the posterior brain regions, suggesting a degeneration of axons passing through focal lesions and areas of demyelination (Rocca et al., 2014). The cerebellar cortex is affected early in MS which, in turn, may result in a failure of patients to recruit this structure, as suggested by findings in the present study (Calabrese et al.,

2010). A decrease in performance between controls and patients may not have been seen as a result of the fact that the Go/No-go is a simple task of inhibition and patients are still capable of performing this task fairly well even without the support from the cerebellum. If the inhibitory-response task became more complex it is possible that the lack of contribution from posterior brain regions, such as the cerebellum, would have had a notable functional impact on the patients' performance.

Limitations. First, both patients and controls made very few errors due to the low cognitive demand of the simple Go/No-go task, with accuracy ranging from 92-100% in controls and 91-99% in patients. It is possible that the green "go" stimulus and the red "no-go" stimulus are so familiar that recognition of these two stimuli has become part of an automatic response, requiring very little 'executive control' by the participants. Therefore, the results may have been limited by a ceiling effect. As such, certain activation patterns may not have been observed in the current study since the task was not difficult for either group.

Second, while the whole brain approach could potentially provide more information on many different areas involved in response inhibition, this approach also provides significant activation patterns that result from Type 1 error from the sheer number of comparisons made between voxels.

Conclusion

In the present study, both patients and controls performed similarly on a simple Go/No-go. Lower accuracy on the Go/No-go task trended with younger age at disease onset and higher lesion volume, suggesting that patients with a young onset of disease and/or higher lesion burden are less proficient in terms of response inhibition. In the present study, controls showed greater activation than patients in the cerebellum, brainstem, lateral occipital cortex, parahippocampal

gyrus, precuneus, superior parietal lobe, precentral gyrus and superior frontal gyrus. These differences may have been observed as result of the diffuse damage to the posterior regions of the brain known to be affected in pediatric-onset MS patients. Despite these significant differences in activation patterns, patients were able to perform the GNG task as well as controls. The present results suggest that MS is impacting a widespread functional network, including both frontal and posterior brain regions that are involved in response inhibition.

Although a direct comparison between our fMRI results and structural results were not possible in the present study, future work should determine if the observed results are consistent with those of previous studies examining topographic changes in white and gray matter (Kerbrat et al., 2012; Mesaros et al., 2008). Future work should also examine how greater brain lesion volume correlates with activation in the frontal regions, which are known to play an important role in decision-making and response inhibition (Bonnet et al., 2010; Bechara et al., 2000). This will assist in providing insight into the disease progression hypothesis. Future studies can also examine functional reorganization and the influence of age at disease onset and degree of brain pathology by using a longitudinal design.

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