A FEASIBILITY STUDY OF WORKING MEMORY TRAINING FOR INDIVIDUALS WITH PEDIATRIC-ONSET MULTIPLE SCLEROSIS

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Abstract

Cognitive impairment occurs in up to half of children and adolescents with multiple sclerosis (MS), and may be severe enough to compromise intellectual functioning, academic performance, and daily life function. Working memory (WM), which refers to the cognitive system that temporarily stores information long enough to use while manipulating the information for some purpose, is one of the major executive functions found to be compromised in pediatric-onset MS patients. The current dissertation sought to introduce a computerized cognitive training program (Cogmed) that is novel to the MS population in order to investigate feasibility, subjective experiences, and individual characteristics related to training outcomes, as well as examine preliminary efficacy of Cogmed in pediatric-onset MS patients. This dissertation employed mixed methods comprising Cogmed-specific training outcomes, performance on pre- and post-training neuropsychological assessment measures, and patient exit interviews. Pediatric-onset MS individuals who were identified as having cognitive difficulties (n = 9) underwent 5-6 weeks of intensive, home-based computerized training on verbal and visual-spatial WM exercises. Patients demonstrated general adherence and tolerance to Cogmed training, and completed training within the recommended 5-6 week timeframe. Almost all patients acknowledged changes in their WM performance as a result of training (n =8), and all patients (n = 9) described the training program as not intruding on their social lives. Age, disease onset, disease duration, and degree of brain atrophy emerged as potential predictors of individual training outcomes, as did intrinsic motivation. All individuals demonstrated improved performance on trained measures of WM and three individuals demonstrated improved performance on select non-trained measures of WM. The findings of this study demonstrate feasibility of implementing Cogmed in pediatric-onset MS patients, warranting subsequent large-scale randomized

controlled studies that employ a multimodal approach to data analysis and that pay attention to individual differences that may predict variable training outcomes.

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Overview

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) that can lead to physical, sensory, psychiatric, and cognitive symptoms of varying severity. Pediatric-onset MS (i.e., onset of MS prior to age 18) affects 1.4 to 2.5 per 100,000 Canadian children. Cognitive impairment occurs in up to half 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; Benedict et al., 2004; MacAllister et al., 2005; MacAllister et al., 2007; Till et al., 2011b). While cognitive impairment is the most disabling deficit accompanying the early stages of pediatric-onset MS, there is a paucity of research investigating effective interventions for the treatment or prevention of cognitive impairment. Research to date has focused on the identification and characterization of cognitive impairment, but there is no established treatment. Gains in working memory (WM) performance, through intensive computerized training, have been demonstrated in other pediatric populations with brain injury. The current study sought to introduce a methodology of a cognitive training program (Cogmed) that is novel to the MS population in order to investigate the feasibility, subjective experiences, and individual characteristics related to training outcomes, as well examine preliminary efficacy of Cogmed in individuals with pediatric-onset MS. The purpose of the current study was to investigate whether targeted WM training may serve as a potential intervention to help reduce the burden of cognitive symptoms, maximize functioning of individuals, and optimize quality of life for those living with pediatric-onset MS.

Chapter One: Introduction

Section 1: Overview of Pediatric Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) that can lead to physical, sensory, psychiatric, and cognitive symptoms of varying severity. MS is characterized by widespread lesions, or plaques, in the brain and spinal cord that affect the myelin sheath, and subsequently, disrupt axonal transmission. Prevalence rates of MS tend to vary by continent and geographical latitude, with high prevalence rates reported in North America and northern parts of Europe (greater than 30 per 100,000); medium prevalence rates in southern Europe and southern United States (5-30 per 100,000); lower prevalence rates in Central and South America (10-20 per 100,000); and lowest prevalence rates in Asia (less than 5 per 100,000) (Koch-Henriksen & Sorensen, 2010). The three factors that appear to influence MS prevalence include population genetics, the interplay between genes and geographically determined physical environment, and socioeconomic structure (Koch-Henriksen & Sorensen, 2010; Kurtzke, 1965). Canada has one of the highest prevalence rates of MS worldwide, affecting 250 per 100,000, with 5 – 15% of these individuals being diagnosed prior to age 18 (Yeh et al., 2009a). Pediatric MS affects 1.4 to 2.5 per 100,000 Canadian children. Gender ratios in pediatric MS appear to differ with age at onset, with a ratio of 0.8:1 females to males reported for children under the age of 6 years, which increases to 1.6:1 between the ages of 6-10 years, and then 2.1:1 for children over 10 years of age (Banwell, Ghezzi, Bar-Or, Mikaeloff, & Tardieu, 2007). It is unknown whether the significant increase in female preponderance in adolescence is largely due to hormonal influence, gender-specific genetic influence on immunological reactivity, or some other age-related factor. Pediatric MS study groups across centers have observed more racial and ethnic diversity in pediatric-onset MS, compared to the adult MS population (Kennedy et al., 2006). In comparison to the adult MS population, African American children have been reported as being more vulnerable to the disease than Caucasian children (Chitnis & Pirko, 2009).

MS presents almost exclusively as a relapsing-remitting disease in children, referred to as relapsing-remitting MS (RRMS) (Banwell et al., 2007). More than 97% of patients with pediatric-onset show this presentation (Boiko et al., 2002), which is characterized by unpredictable and isolated relapses, during which the new symptoms appear and existing ones worsen, followed by periods of complete or near complete recovery. Of note, pediatric-onset MS presents as a more inflammatory disease that is characterized by a 2-3 times higher relapse rate than in adults (Gorman, Healy, Polgar-Turcsanyi, & Chitnis, 2009), though recovery from these initial clinical attacks is usually excellent. In contrast, the progressive types of MS are characterized by an accumulation of symptoms over time, with the primary subtype of MS occurring from disease onset, and the secondary subtype typically occurring 10-20 years following the diagnosis of RRMS and in approximately 50% of these individuals (Boiko et al., 2002; Weinshenker et al., 1989). In children, the time to reach the secondary progressive stage is longer. However, because of the young onset of the disease in pediatric MS, this stage is ultimately met at a younger age than adults with MS. Please see **Figure 1** for the four subtypes of MS.

Clinical features of the initial attack of pediatric-onset MS include polyfocal or polysymptomatic presentation in 50-70% of children and monofocal presentation in 30-50% (Mikaeloff et al., 2004; Ozakbas, Idiman, Baklan, & Yulug, 2003). Pediatric-onset MS patients tend to have a polyfocal onset of symptoms in comparison to adult MS patients (Gorman et al., 2009). Clinical features of the initial attack may include motor dysfunction, sensory symptoms, ataxia, gait problems, or brainstem symptoms (Ghezzi et al., 2002; Ozakbas et al., 2003). Optic nerve involvement appears to become more frequent with increasing age (Ruggieri, Polizzi, Pavone, & Grimaldi, 1999).

Fatigue is reported by 40% of individuals with pediatric-onset MS, and seizures occur in 5%, however, they appear to be more common in children under 10 years of age where they can occur in almost 25% (Ruggieri et al., 1999). While fever has been reported as a presenting feature in one-fourth of MS patients under the age of 10 years, this seems to be a rare feature in older patients. Younger MS patients are also more likely to present with widespread demyelination on magnetic resonance imaging (MRI), polyfocal clinical features, and encephalopathy (Banwell et al., 2007).

Though the cause of MS is still unknown, it is believed - as with many complex diseases - to reflect an interaction between genetic susceptibility and environmental risk factors. In terms of risk factors, epidemiological research suggests that the risk of MS is heavily influenced by one's place of residence during childhood (Pugliatti et al., 2006), particularly early childhood. Results of migration studies in adult-onset MS suggest that individuals who emigrate during childhood to areas of elevated MS risk go on to assume the risk of MS associated with their adopted home (Dean & Elian, 1997). For example, one study in particular (Dean & Elian, 1997) found that Indian and Pakistani immigrants who immigrated to England when they were younger than 15 years of age had a higher risk of developing MS than those who immigrated after this age. Research suggests that childhood viral exposures may have a role in the MS disease process (Marrie et al., 2000; Pugliatti et al., 2006). There is documented evidence of remote infection with Epstein Barr virus in over 85% of children with MS, compared to only 40-60% of age-matched, healthy children (Banwell et al., 2007; Pohl et al., 2006). However, not all children with MS are positive for Epstein Barr virus nor do all children who are positive for Epstein Barr virus have MS, indicating that this risk factor has very low sensitivity and if MS is triggered by infection, then other infections must be implicated. One study of common viruses in childhood found that a remote cytomegalovirus (CMV) infection was independently associated with a *lower* risk of MS, suggesting a potential complex interplay between various viral infections during childhood and MS risk/protection (Waubant et al., 2011). Vitamin D insufficiency has also emerged as a risk factor for susceptibility to MS (Munger, Levin, Hollis, Howard, & Ascherio, 2006). Recent research has identified a vitamin D response element in the promoter region of *HLA-DRB1*15* haplotypes (Ramagopalan et al., 2009) (which are considered to be the main susceptibility alleles for MS), particularly *HLA-DRB1*1501* (Oksenberg et al., 2004). Furthermore, vitamin D insufficiency has been associated with substantially increased relapse rates in individuals with pediatric-onset MS (Mowry et al., 2010), though recent evidence implicating vitamin D in the onset of MS has been weak. As with adult MS, exposure to cigarette smoke may increase MS risk in children; relative risk for an initial episode of MS in a child exposed to smoking has been found to be more than double of that of the control population (Mikaeloff, Caridade, Tardieu, & Suissa, 2007). The underlying mechanism in this case may involve either direct toxic effects of cigarette smoke on the blood-brain barrier or central nervous system, or some sort of nicotine effect on vascular blood flow within the brain. Though vaccinations have often been suggested as potential triggers of MS, recent studies have not shown an association between the hepatitis B vaccine and recurrent demyelination in either children or adults with MS (Confavreux, Suissa, Saddier, Bourdes, & Vukusic, 2001; Mikaeloff, Caridade, Assi, Tardieu, & Suissa, 2007). Family history of MS has been reported by 6-8% of individuals with pediatric-onset MS (Mikaeloff et al., 2004; Ozakbas et al., 2003; Sadovnick & Ebers, 1993).

The individuals with pediatric-onset MS studied in this dissertation were diagnosed according to the 2010 revised McDonald criteria (described in the manuscript of Polman et al., 2011). Diagnosis of RRMS in pediatric patients rests on meeting the criteria of both dissemination in space (DIS) and dissemination in time (DIT) using clinical and MRI findings (Poser et al., 1983). MRI findings can be used to define DIS based on one or more T2 lesion(s) in at least two of four following areas of the CNS: periventricular, juxtacortical, infratentorial, and spinal cord.

According to the International Pediatric Multiple Sclerosis Study Group's revisions to the 2007 definition (Krupp et al., 2013), a diagnosis of pediatric-onset MS can be satisfied by <u>any</u> of the following criteria:

1) Two or more non-encephalopathic (i.e., not acute disseminated encephalomyelitis (ADEM)-like), clinical CNS events with presumed inflammatory cause, separated by more than 30 days (i.e., clinical relapse evidence of DIT) and involving more than one area of the CNS (i.e. clinical DIS);
2) One non-encephalopathic episode typical of MS which is associated with MRI findings consistent with the 2010 Revised McDonald criteria for DIS and in which a follow-up MRI shows at least one new enhancing or non-enhancing lesion consistent with DIT MS criteria (Polman et al., 2011);

3) One ADEM attack followed by a non-encephalopathic clinical event, three or more months after symptom onset, that is associated with new MRI lesions that fulfill 2010 Revised McDonald DIS criteria (Polman et al., 2011);
4) For children age 12 or older, a first, single, acute event that does not meet ADEM criteria and whose MRI findings are consistent with the 2010 Revised McDonald criteria for DIS and DIT.

With respect to MRI characteristics, at the time of initial clinical presentation of a CNS demyelinating event, MRI findings which are indicative of MS include lesions in a periventricular location, hypointense lesions on T1 imaging, and absence of bilateral diffuse lesions (Callen et al., 2009; Mikaeloff et al., 2004; Verhey et al., 2011). Compared to adults with similar disease duration, pediatric-onset MS patients show higher T2 lesion volume, more lesions in the posterior fossa, infratentorium, and cerebellum (Chitnis et al., 2013), and lesions tend to accrue more quickly (Yeh et al., 2009b). Despite this heightened lesion accrual, disability accrual tends to be slower in pediatric-onset MS patients than in adult-onset MS patients (Chitnis, 2013) with a median time from disease onset to conversion to secondary progressive MS being 20 years in pediatric-onset MS and 10 years in adult MS (Renoux et al., 2007). Suggested hypotheses (and areas of active study) are that the areas associated with locomotor disability are less likely to be affected in pediatric-onset MS or that recovery and repair mechanisms in these individuals are enhanced (as a result of being in the active stage of remyelination) in comparison to their adult counterparts (Chitnis, 2013). The median time to reach relative severe disability, as indexed by an Expanded Disability Status Scale (EDSS) score of 4, is 20 years in pediatric-onset MS and 10 years in adult MS (Renoux et al., 2007). Despite the longer time for pediatric-onset MS patients to show disability, the average age at which irreversible disability occurs is 10 years younger than adults given the significantly younger age at disease onset (i.e., average age of disease onset is 14 years in pediatric-onset MS versus 30 years in adult MS). White matter integrity appears to be decreased in pediatric-onset MS patients in all regions of the brain, with the exception of the frontal lobes, likely due to their protracted development (Till et al., 2011a).

Treatment of MS usually involves a combination of pharmacological/disease-modifying therapies, as well as other medications and supportive treatments. Disease-modifying therapies have been shown to prevent future relapses, slow disability progression, and reduce lesion accrual. While disease-modifying therapies have not been shown to improve cognition, there is some research to suggest that they may stabilize cognitive performance by preventing further atrophy. Standard treatment for an MS relapse is corticosteroids; if steroids are found to be ineffective in the presence of severe relapses, plasmapheresis or intravenous immunoglobulin may be options (MacAllister et al., 2013). There is consensus that pediatric MS should be treated with disease-modifying agents soon after diagnosis is confirmed (Chitnis et al., 2012). Medications for specific symptoms (e.g., fatigue, pain, depression, spasticity) are also commonly prescribed in pediatric MS.

Section 2: Cognitive Dysfunction in Multiple Sclerosis

Cognition in adults with MS. Much of our existing knowledge with respect to the effects of MS on cognition, predictors of cognitive impairment (CI), and how these deficits can be treated with various rehabilitation approaches, is informed by adult MS research. MS research over the past three decades has consistently shown that CI is common in adults with MS, with prevalence rates ranging from 43 to 70% (Benedict et al., 2006; Peyser, Rao, LaRocca, & Kaplan, 1990). Cognitive dysfunction has been found to be closely associated with functional status in MS, such that cognitively impaired MS patients participate in fewer vocational and social activities and are less likely to be employed (Rao et al., 1991).

The various aspects of cognitive functioning that are affected in MS include processing speed (DeLuca, Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004), long-term memory (Brassington & Marsh, 1998; DeLuca, Barbieri-Berger, & Johnson, 1994; Rao et al., 1993), attention (Beatty et al., 1996; Litvan et al., 1998) and executive functioning (Denney, Sworowski, & Lynch, 2005; Lazeron, Rombouts, Scheltens, Polman, & Barkhof, 2004). Reduced speed of processing has been found to be the most common cognitive deficit in MS (Bergendal, Fredrikson, & Almkvist, 2007; Denney, Lynch, Parmenter, & Horne, 2004; DeLuca et al., 2004; Janculjak, Mubrin, Brinar, & Spilich, 2002) and impairments in processing speed are typically seen in co-occurrence with other cognitive deficits in working memory (WM) and long-term memory (Gaudino, Chiaravalloti, DeLuca, & Diamond, 2001; Janculjak et al., 2002; Lengenfelder, Chiaravalloti, Ricker, & DeLuca, 2003). Deficits in both WM and processing speed appear to affect each other in adults with MS, such that as the demands on WM increase, deficits in both speed of processing and WM become prominent (Lengenfelder et al., 2006). Furthermore, in some studies the extent of memory impairment has been positively correlated with deficits in processing speed (DeLuca et al., 2004; Gaudino et al., 2001). It is important to bear in mind that deficits in memory exist in MS over and beyond reduced processing speed, such that if the processing speed component on tasks was removed, WM impairments would still remain. In addition to reduced processing speed, WM and long-term memory impairments in adults with MS have also been widely reported (e.g., D'Esposito et al., 1996; Diamond et al., 1997; Lengenfelder et al., 2003; Ruchkin et al., 1994; Wishart & Sharpe, 1997). WM impairments in MS patients are thought to reflect an impaired “central executive system” – an attentional control system that coordinates, controls, and manipulates information processing (D'Esposito et al., 1996; Lengenfelder et al., 2003). With respect to long-term memory impairments, earlier MS research suggested that the nature of the memory deficit was due to difficulties in retrieval, while more recent research has demonstrated that the primary problem is in the initial learning of information (DeLuca et al., 1994; DeLuca, Gaudino, Diamond, Christodoulou, & Engel, 1998; Thornton, Raz, & Tucke, 2002). When learning verbal material in particular, MS patients appear to require more repetitions of information (DeLuca et al., 1994).

Although simple attention tasks (e.g., digit repetition) are typically unaffected in patients with MS, impairments in sustained attention appear to be more common (Beatty, Paul, Blanco, Hames, & Wilbanks, 1995), and decrements in divided attention have also been reported (McCarthy, Beaumont, Thompson, & Peacock, 2005). Although less frequent than deficits in processing speed and long-term memory, deficits in executive functions do occur in patients with MS (Bagert, Camplair, & Bourdette, 2002; Bobholz & Rao, 2003; Brassington & Marsh, 1998). More specifically, deficits have been found in both phonemic and semantic fluency (Henry & Beatty, 2006), and perseverative errors are common in patients with MS (Arnett, Rao, Bernardin, Grafman, Yetkin, & Lobeck, 1994a; Parmenter et al., 2007). Limited research has been done with respect to visual perceptual processing in patients with MS, however, up to a quarter of individuals with MS may have deficits in this area (Denney et al., 2004). Most studies indicate that general intelligence remains intact in patients with MS Macniven et al., 2008). Pragmatic verbal skills (i.e., word naming and comprehension) are usually not affected in MS (Rao, Leo, Bernardin, & Unverzagt, 1991).

Finally, it is important to consider the impact of psychosocial factors on cognitive functioning in MS patients. Research suggests that major depression in MS patients may exert a deleterious effect on cognitive functioning, particularly those aspects related to executive function (Feinstein, 2006). The relationship between depression and impaired cognition appears to reflect a pattern whereby depression may lead to impaired cognitive and attentional capacity which may contribute to executive dysfunction, including working memory deficits (Feinstein, 2006). The deleterious effect of depression on cognitive functioning is concerning, given that the lifetime prevalence of major depression in MS adult patients approaches 50%, which is considerably elevated in comparison to that of the general population and most other neurological disorders (Sadovnik et al., 1996; Schubert & Foliart, 1993). Fatigue is one of the most common and disabling symptoms in MS that has been reported by 53-90% of patients (Janardhan & Bakshi, 2002). Individuals with MS frequently report that fatigue affects their cognitive functioning (Krupp & Elkins, 2000).

Cognition in children and adolescents with MS. While research on cognition in adult MS can definitely help to inform our understanding of cognition in pediatric-onset MS, caution must be taken to not simply extrapolate cognitive outcomes in adults to children. In pediatric-onset MS, the impact on cognitive functioning could be even more dramatic than that observed in adult-onset cases because the inflammation and demyelination occur during a critical time when neuronal networks are being established (Portaccio et al., 2010).

Cognitive functioning in pediatric-onset MS is less well described, and there are only a handful of studies which have attempted to do this. CI occurs in 31-53% 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). Cognitive deficits can be detected across multiple domains, including memory, attention, executive functions, and information processing speed, as well as some aspects of visual-motor function and language (Amato et al., 2008; Banwell & Anderson, 2005; Benedict et al., 2004; MacAllister et al., 2005; MacAllister et al., 2007). These deficits can be observed even early in the disease and variable profiles may reflect a number of factors, such as timing of the disease and/or severity of disease and its predilection for cognitively-relevant networks (Rocca et al., 2014a). In support of an early vulnerability perspective, cross-sectional studies in pediatric MS have associated younger age at disease onset with worse cognitive performance (Amato et al., 2008; Banwell & Anderson et al., 2005) and poorer parent ratings of child executive skills (Till et al., 2012).

One North American study described 37 children and adolescents with MS and investigated predictors of cognitive dysfunction (MacAllister et al., 2005). Cognitive dysfunction, characterized as two or more tests out of ten falling at least 1.5 standard deviations below age-matched normative data, was seen in over a third of this group. In specific cognitive domains, 38% of the group showed attentional impairments, 21% showed poor confrontation naming, 15% showed deficits in verbal comprehension, 21% presented with verbal memory deficits, and 12% showed visual memory deficits. Furthermore, neurologic dysfunction (defined by impairment in functional systems, and measured by score on the Expanded Disability Status

Scale (EDSS; Kurtzke, 1983)[1], total number of relapses experienced, and overall disease duration were found to all correlate with cognitive function; neurologic dysfunction was identified as the strongest predictor of overall cognition (Till et al., 2011b; MacAllister et al., 2005). It is important to note, however, that other studies have not shown a correlation between neurologic dysfunction and cognitive dysfunction, likely reflecting the low incidence of physical disability in pediatric-onset MS.

A seminal 2008 Italian study described cognitive outcomes in 63 children and adolescents with MS (Amato et al., 2008). Consistent with the results of the previous study, one third of this group showed significant cognitive dysfunction, with visuospatial memory, complex attention, verbal comprehension, and executive functions being the most frequently impaired cognitive functions in this group. As noted above, young age at onset was also found to be a significant predictor of cognitive dysfunction in this group.

A more recent 2011 North American study described cognitive outcomes in 35 pediatric-onset MS patients and attempted to identify MRI correlates of CI (Till et al., 2011b). Mean cognitive scores were found to be significantly reduced on 9 of 19 outcomes in the MS group, compared to healthy controls. Areas predominantly affected were attention, processing speed, visuomotor integration, and most aspects of expressive language. With respect to intellectual ability, overall IQ and verbal IQ were significantly reduced in the MS group compared to demographically-matched controls (however, overall means fell within the average range). Additionally, higher IQ was found to be associated with shorter duration of disease and older age

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[1] Though the EDSS is purely a measure of *neurologic dysfunction*, this term is often used interchangeably with *physical disability* because the degree of neurologic dysfunction tends to predict the degree of physical disability.

at disease onset. This study also documented strong associations between cognitive deficits and reductions in the size of the thalamus and total brain volume.

Deficits in executive functions are particularly vulnerable to disruption given the tendency of the disease to affect diffuse neuronal networks that underlie these complex cognitive skills (Casey, Tottenham, Liston, & Durston, 2005). Moreover, because executive function skills continue to mature throughout childhood and adolescence, difficulties in executive function may emerge over time as these individuals 'grow into a deficit' (Dennis, 1999; Levin, Song, Ewing-Cobbs, Chapman, & Mendelsohn, 2001). In children and adolescents with MS, executive dysfunction has been commonly reported, though the extent of impairment varies across tests and across studies. Working memory (WM), which refers to the cognitive system that temporarily stores information long enough to use while manipulating the information for some purpose, is one of the major executive functions found to be compromised in pediatric MS patients (Amato et al., 2008; MacAllister et al., 2005; Till et al., 2011b). Recent results reported by various groups (MacAllister, 2010; Till et al., 2011b) show that approximately half of pediatric MS patients demonstrate problems in WM, and up to half of all patients in a group of 44 patients were reported by parents as having clinically significant difficulties in everyday executive function behaviours. In this study, parents most frequently reported concerns in their child with regard to WM, planning/organization, and emotional control. Given the reliance of WM on efficient processing, it has been proposed that difficulties in WM may emerge or be exacerbated as a consequence of a primary processing speed deficit that frequently characterizes MS patients (Drew, Starkey, & Isler, 2009).

In addition to WM difficulties, difficulties on neuropsychological measures of cognitive flexibility, such as the Contingency Naming Test and Part B of the Trail Making Test, occur in up to 50% of children and adolescents with MS (Deery, Anderson, Jacobs, Neale, & Kornberg, 2010; MacAllister et al., 2005; Till et al., 2011b). Impaired verbal fluency has also been reported in some studies of childhood-onset MS (Banwell & Anderson, 2005; Till et al., 2011b), but not in others (Deery et al., 2010; MacAllister et al., 2005; Portaccio et al., 2009). Children and adolescents with MS have also been shown to demonstrate deficits on non-timed measures of problem solving and concept formation, such as the Modified Card Sorting Test (Amato et al., 2008) and the Tower of London (MacAllister, 2010) but not on the Wisconsin Card Sorting Task (Banwell & Anderson, 2005; Till et al., 2011b).

Fatigue in children and adolescents with MS. As with adult MS patients, fatigue is a significant issue in pediatric-onset MS that is reported in up to three-quarters of pediatric-onset MS patients, even early in their disease course (Amato et al., 2010). MS-related fatigue can be classified as either primary or secondary. Primary fatigue is thought to be due to disease-related aspects including inflammation and demyelination. Secondary fatigue results from factors such as poor sleep, bladder disturbance, depression, lack of exercise, medication side effects and/or cognitive/mental exertion. Higher levels of self-reported cognitive fatigue in pediatric-onset MS patients has been associated with impaired performance on prolonged/cognitively effortful tasks, as well as more sleep problems and emotional and academic difficulties (Goretti et al., 2012).

Psychiatric features in children and adolescents with MS. Psychiatric problems are also commonly reported in pediatric-onset MS. In the study of MacAllister and colleagues (2005), six (46%) of 13 patients who underwent psychiatric evaluation were diagnosed with an affective disorder including major depressive disorder and anxiety disorder. In an Italian sample of 39 pediatric MS patients (Amato et al., 2010), psychiatric interview revealed the following: major depression in 15%, depression and anxiety in 5%, panic disorder in 5%, and bipolar disorder in 5%. Importantly, these authors noted that the prevalence of depression (measured using the Children Depression Inventory) increased from 6% at baseline to 17% at 2-year follow-up. In a study of 45 pediatric MS patients by Weisbrot and colleagues (2014), 56% of patients met criteria for at least one psychiatric diagnosis, with 68% of these patients receiving at least two or more diagnoses. The most common categories of psychiatric diagnoses were anxiety disorders (33%), attention deficit hyperactivity disorder (27%), and mood disorders (24%), assessed using semi-structured psychiatric diagnostic interviews. In summary, psychiatric disturbances are prevalent in the pediatric MS population, especially depression and anxiety, supporting appropriate screening and management. In summary, pediatric-onset MS patients differ in their cognitive profiles as compared with adults with MS. Pediatric-onset MS patients are more likely to show lower IQ and impairments in language, while these two areas of cognition are typically preserved in adults with MS. These differences are likely due to the impact of the disease on developing networks in children and adolescents in contrast to established networks in adults. As with adults, pediatric-onset MS patients demonstrate impairments in executive functions, including WM. More specifically, up to half of all pediatric-onset MS patients have difficulties with WM. This is concerning, given the wide range of involvement of WM in cognitive and academic activities. In pediatric-onset MS, identified clinical predictors of cognitive dysfunction include greater number of relapses, longer disease duration, young age at onset

Neural correlates of cognitive dysfunction in pediatric-onset MS. Given the well-known role of myelin in learning and information processing (Fields, 2008), the focus of research in pediatric-onset MS has previously been on how white matter (WM) lesions and demyelination impact the development of the CNS. While lesions visible on MRI are integral to the diagnosis of MS, lesion volume has proven to be a surprisingly poor indicator of cognitive impairment. One reason for the poor association between total lesion volume and clinical disability is the possibility that disease-related pathology is occurring in a more general way throughout the brain (e.g., atrophy) and thus focusing exclusively on lesions, especially T2 lesions given their fluctuating and often transient nature, may not directly relate to the severity of a patient's deficits. Another reason is that the brain may adapt to lesions seen on MRI by routing neural impulses around hyperintense regions that are actively under attack by the immune system through the use of compensatory mechanisms. Moreover, the specificity of the lesion volume metric is poor because it lacks detail with respect to the spatial location and size of lesion (i.e., a lesion volume of 10 cubic centimeters could reflect 5 large lesions or 20 small lesions), which in turn, will result in a different clinic-pathologic relationship. In an attempt to control for spatial location of lesions, studies have examined the contribution of regional lesion volume (as opposed to global lesion volume) to specific patterns of cognitive dysfunction (Till et al., 2012); however, results of these studies did not prove more sensitive than global lesion volume, likely reflecting the fact that lesional distribution is not focal and hence it is impossible to tease out the diffuse injury to the brain. As with adult MS, T2 lesion volume appears to show stronger correlations with specific neuropsychological outcomes than does T1 lesion volume, perhaps in part due to the more focal nature and smaller size of T1 lesions relative to T2 lesions. Moreover, most studies examining the association between lesion volume and cognitive performance are based on an MRI scan taken at one time point. It is not clear whether T1 lesions in these studies represent areas of permanent insult or transient hyperacute lesion formation. While the traditional way of thinking is that MS is primarily a white matter disease, more recent research has identified gray matter (GM) pathology as making a considerable contribution to cognitive dysfunction in pediatric-onset MS (Aubert-Broche et al., 2011; Kerbrat et al., 2012). Through regression analyses, one study in particular (Till et al., 2011b) identified GM as the best predictor of IQ and information speed, such that global brain volume loss in GM was associated with lower estimated IQ and slower information processing speed. WM volume, on the other hand, did not enter the regression model, suggesting that GM volume accounted for the greatest amount of variance in predicting cognitive function. Another study revealed severe damage to the GM, particularly in the right precuneus and left middle temporal gyrus, in cognitively-impaired patients in comparison with cognitively-preserved patients (Rocca et al., 2014b). Moreover, such associations were evident within early stages of the disease, thus highlighting the detrimental impact of neurodegenerative disease on cognitive development. In another study, the thalamus was examined in 35 individuals with pediatric-onset MS, given its integrative role in various cognitive abilities (i.e., attention, arousal, memory, speeded information processing) as well as its susceptibility to MS pathology (Mesaros et al., 2008). The thalamus turned out to be the most robust MRI predictor of global functional outcomes, as well as measures of mental processing speed, visuomotor integration, and vocabulary (Till et al., 2011b). Moreover, in this same sample of MS patients, atrophy of the thalamus and frontal lobe volume predicted executive dysfunction (Till et al., 2012). Together, these findings highlight the crucial role of the thalamus in a variety of cognitive abilities as well as the dramatic impact of damage to thalamic circuits in this vulnerable population.

Functional MRI studies have begun to elucidate the concept of neural reserve (Rocca et al., 2009) as well as changes to cognitively-relevant networks in pediatric-onset MS (Rocca et al., 2014b; 2014c). Compared with healthy controls, pediatric-onset MS patients demonstrated decreased functional connectivity (FC) in various areas of sensory- and cognitive-related resting-state networks (particularly in more posterior brain regions), thus suggesting impaired maturation of brain connectivity (Rocca et al., 2014c). Interestingly, increased FC was found in the medial frontal gyrus (implicating the attention network and also the default network), and such increased FC was inversely correlated with T2 lesion volume and pronounced in cognitively-preserved patients. This finding suggests that increased FC may, at least partially, serve to counteract disease-related abnormalities when structural damage is relatively modest, whereas this mechanism is more likely to fail with accumulating structural abnormalities. Likewise, in another study (Rocca et al., 2014b), decreased resting-state FC of the precuneus was found in cognitively-impaired patients in contrast to higher resting-state FC of the anterior cingulate cortex in cognitively-preserved patients. Such a finding lends support to the concept of functional reorganization processes to delay functional decline.

Section 3: Overview of Study

To date, research has focused on the identification and characterization of cognitive impairment in pediatric-onset MS. While cognitive difficulties are the most disabling deficit accompanying the early stages of pediatric-onset MS, there is currently no established effective pharmacological treatment for cognitive dysfunction (DeLuca & Nocentini, 2011). Moreover, there is a paucity of research investigating effective interventions to prevent these patients from experiencing later adverse cognitive sequelae – and in particular executive dysfunction. To our knowledge, there is only a single case report in the literature examining the efficacy of a cognitive intervention program for a child with MS (Amato, 2011).

It is proposed that working memory (WM) be targeted in pediatric-onset MS patients given: (1) consistent reports of WM dysfunction in this population (Amato et al., 2008; Till et al., 2011b); (2) the tendency of the disease to affect diffuse networks and brain regions associated with WM (Bethune et al., 2011); and (3) increasing evidence that WM capacity can be improved by adaptive and extended training (Klingberg, 2010a). Thus, the purpose of the present study was to introduce a cognitive training program that is novel to the MS population in order to investigate the feasibility of conducting cognitive rehabilitation with individuals with pediatric-onset MS, explore the subjective experiences of those who complete the training program, and identify individual predictors of training outcomes. Secondary to this aim, the current study sought to investigate the potential efficacy of the program. The training program is called Cogmed and is designed to target WM. An overview of WM and its development will first be presented. This will be followed by a summary of the cognitive rehabilitation literature in adult MS with a focus on the changes that have been documented at both the behavioural and neural level and the possible mechanisms that may be underlying these effects, as well as the subjective experiences of those who engage in rehabilitation. Next, the response to Cogmed training in various adult and pediatric populations will be reviewed. Finally, individual characteristics which may moderate receptivity or tolerability to cognitive rehabilitation will be discussed.

Section 4: Working Memory

Multi-component model of working memory. WM is a system that allows one to temporarily hold information in mind long enough to use, while manipulating the information for some purpose (Baddeley, 2000). WM has been described as a critical ability that is necessary for many cognitive tasks, such as remembering instructions and completing tasks, and is also implicated in practical applications such as academic learning, language comprehension, and reasoning (Gathercole, Pickering, Ambridge, & Wearing, 2004; Geary, Hoard, Byrd-Craven, & Catherine DeSoto, 2004; Nigg, 2006)). Examples of WM include comprehending a complex sentence and mentally rotating an unfamiliar geometric figure – these activities critically depend on one's ability to store various intermediate products of some computation while *simultaneously* processing new incoming information (Shah & Miyake, 1996). It is this latter part – simultaneously processing new information – that distinguishes WM from short-term memory which only involves storage of information for short periods of time. According to an influential WM model first proposed by Baddeley & Hitch in 1974 (Baddeley & Hitch, 1974), WM consists of three components: two storage systems (the phonological loop and the visuo-spatial sketchpad) and one control system (the central executive). Please see **Figure 2**. The model was extended further with the addition of a fourth component known as the episodic buffer (Baddeley, 2000). The four components will be described in more detail below.

According to Baddeley and Hitch (1974) the phonological loop is responsible for the storage and maintenance of information in a phonological form, while the visuo-spatial sketchpad is responsible for storage and maintenance of visual and spatial information (Repovs & Baddeley, 2006a). The phonological loop is further subdivided into two sub- components: a phonological store – which holds memory traces in either acoustic or phonologic form that fade within a few seconds; and an articulatory rehearsal process which is comparable to subvocal speech (Baddeley, 1983). The articulatory rehearsal process functions to refresh the memory trace by retrieving and re-articulating the contents of the phonological store. Lesion studies suggest that the neuroanatomical basis for the phonological store is the inferior parietal cortex, while the articulatory rehearsal process relies on brain areas necessary for speech production (i.e., Broca's area, the supplementary motor association area, and possibly the cerebellum) (Muller & Knight, 2006). Developmentally, the phonological store appears to be in place by 3 years of age (Gathercole & Adams, 1993), while the articulatory rehearsal process does not seem to emerge until about 7 years of age (Gathercole & Hitch, 1993).

The existing model of the visuospatial sketchpad is less understood than the phonological loop model described above, but research has shown that the visuospatial sketchpad is not a unitary system and that it can be further divided into spatial and visual subsystems (Repovs & Baddeley, 2006b). Through a number of double dissociation studies (Hartley, Speer, Jonides, Reuter-Lorenz, & Smith, 2001; Klauer & Zhao, 2004), results have provided clear evidence not only for the existence of separate visual and spatial stores, but also for separate rehearsal mechanisms for visual and spatial information (Repovs & Baddeley, 2006b). Often referred to as the *what* versus *where* distinction, the visual store is thought to be responsible for holding visual shapes and colours, while the spatial store holds locations and movement information (Klauer & Zhao, 2004). Lesion studies suggest that the neuroanatomical basis for the *what* or object recognition system is a ventral stream going from occipital to temporal cortex, whereas the *where* or spatial operations system is a dorsal stream connecting the occipital with parietal cortex (Muller & Knight, 2006).

The central executive is thought to regulate WM in the sense that it directs attention, guides information flow, and coordinates the simultaneous execution of multiple tasks. With respect to WM tasks, the central executive seems to be involved whenever information within the stores requires manipulation, exceeds storage capacity, or requires protection from interference (Repovs & Baddeley, 2006b). Simple representation and maintenance may be independent of this system and are more representative of short-term memory. With respect to complex cognitive abilities, the central executive appears to mainly function as a source of attentional control that permits focusing of attention and division of attention between concurrent tasks.

The episodic buffer serves to integrate information from various sources in the cognitive system, including temporary and long-term memory systems (Gathercole, Pickering, Knight, & Stegmann, 2004). In turn, the integration and maintenance of information within the episodic buffer depends on the central executive (Repovs & Baddeley, 2006a). The multi-component model of WM provides a framework for conceptualizing its role in temporary information storage while concurrently performing a wide range of complex cognitive tasks. Thus, it becomes clear how the function of WM is important in complex cognition, rather than just memory. Poor central executive functioning has been suggested to compromise learning in literacy (de Jong, 1998; Swanson, 1994), vocabulary (Daneman & Green, 1986), and arithmetic (Bull & Scerif, 2001; Passolunghi & Siegel, 2001). There is also direct evidence that WM capacity is a good predictor of mathematic skills (Toll, Van der Ven, Kroesbergen, & Van Luit, 2011), which have been shown to be selectively vulnerable in adolescents and young adults with MS (Till et al., 2011a). Since WM is a fundamental cognitive ability upon which rehabilitation of other functions depends, it is important to address deficits in this area as part of the treatment approach (Malouin, Belleville, Richards, Desrosiers, & Doyon, 2004; Robertson & Murre, 1999b).

Working memory development and brain maturation. When considering neural development in developing humans, the frontal lobes are the last to develop. It has been said that the frontal lobes and the functions supported by the frontal lobes not only differentiate humans from other species, but also adult humans from children and adolescents (Conklin, Luciana, Hooper, & Yarger, 2007). Post-mortem findings have consistently suggested that the frontal lobes continue to develop into the third decade of life, as indicated by a combination of ongoing myelination and pruning, which facilitates more efficient communication among brain regions (Huttenlocher, 1979). Neuroimaging findings have also demonstrated the same pattern of protracted frontal lobe development *in vivo*. For example, one study assessing patterns of brain maturation in adolescents (12-16-year-olds) and young adults (23-30-year-olds) found more maturational changes in the dorsal, medial, and lateral regions of the frontal lobes between adolescence and adulthood than between childhood and adolescence (Sowell, Thompson, Holmes, Jernigan, & Toga, 2000). During this maturational period, little change was observed in the parietal, temporal, and occipital lobes. Such brain maturational changes are supported by behavioural data from studies indicating that performance on various frontal-lobe-specific tasks continues to improve beyond age 12 (Conklin et al., 2007).

Findings from neuroimaging studies have demonstrated that frontal lobe activation is associated with higher-order reasoning skills, referred to collectively as “executive functions”, and include WM (Curtis & D'Esposito, 2003). More specifically, the prefrontal cortex is thought to be the most important substrate for WM (Curtis & D'Esposito, 2003). Different aspects of WM functions have been ascribed to two anatomically distinct areas within the prefrontal cortex: the dorsolateral prefrontal cortex (DLPFC) and ventrolateral prefrontal cortex (VLPRC). A *process-specific* approach suggests that the lateral prefrontal cortex is organized according to the type of processing performed upon information in WM, with the DLPFC only activated by tasks that require active manipulation or monitoring of information (D'Esposito et al., 1998). This theory was upheld in a study of healthy adults (D'Esposito et al., 1998), in which WM tasks requiring active maintenance of information across a non-distracted delay seemed to involve the VLPFC whereas tasks requiring reshuffling of or processing of intervening stimuli during the maintenance of information activated more dorsal substrates.

While component processes of WM may be dissociated neuroanatomically, they may also be dissociated at a developmental level (Conklin et al., 2007). Research findings have demonstrated that typically developing adolescents show improved performance on WM tasks, with performance on tasks involving low central executive processing demands maturing earlier than tasks involving high central executive processing demands (Luciana & Nelson, 2002). More recently, a study investigating WM performance in typically developing children and adolescents found an improvement in performance during adolescence on tasks largely supported by the frontal lobes, but not on tasks supported by more posterior substrates (e.g., recognition memory) (Conklin et al., 2007). The same study also found that while the maintenance and manipulation of multiple verbal units of information was stable after 13-15 years of age (i.e., Digits Span Forward and Letter Span), WM tasks involving increased manipulation (i.e., Digit Span Backward) continued to show change until 16-17 years of age.

In summary, collective findings from neuroanatomical and behavioural studies lend support to a pattern of protracted development of the frontal lobes, and consequentially, WM functions, into adolescence and adulthood. Given that pediatric-onset MS is occurring at a time when the frontal lobes are not yet fully matured, there is increased potential for disruption of functions largely supported by the frontal lobes, such as WM, for which networks have not yet been fully established. Moreover, given that WM is involved in an array of cognitive and academic functions, one can see how critical rehabilitation of WM would be in this population.

Section 5: Cognitive Rehabilitation Training in Adults with Multiple Sclerosis

Within the adult MS literature, a number of studies have examined the efficacy of cognitive training programs designed for the remediation of impairments in the areas of memory, attention, and executive functioning (O'Brien, Chiaravalloti, Goverover, & DeLuca, 2008). Though not extensive, there is some evidence to suggest that computer-assisted cognitive rehabilitation results in improved neuropsychological performance of adults with MS with subjective complaints or objective evidence of cognitive impairment (Stuifbergen et al., 2012). The following section will begin with a review of the literature pertaining to behavioural changes associated with cognitive rehabilitation in adult MS, with particular focus on learning, memory, attention, and processing speed. This will be followed by a review of studies pertaining to neural changes associated with cognitive rehabilitation in MS, and subsequently, other changes (i.e., improvement in quality of life, self-esteem, etc.). Of note, though there are studies focused on memory training in adult MS which use strategy-training, these studies will not be reviewed here. The following review will focus on process-training interventions only.

Learning and memory. A number of studies have demonstrated gains in the domains of learning and/or memory after computer-assisted cognitive rehabilitation in adults with MS (Hildebrandt et al., 2007; Sastre-Garriga et al., 2011; Stuifbergen et al., 2012; Vogt et al., 2009). In a recent randomized controlled study (Stuifbergen et al., 2012), the effects of a home-based computer-assisted cognitive rehabilitation intervention on cognitive performance were explored in 34 adults with MS. The intervention program that was used is called the Memory, Attention, and Problem Solving Skills for Persons with Multiple Sclerosis (MAPSS-MS). Participants in the intervention group performed the computerized intervention for 45 minutes, three times per week for eight weeks. Compared to a wait list control group (*n* = 27), the intervention group typically had greater gains over time across most measures in a neuropsychological battery. In particular, the intervention group showed statistically and clinically significant improvements on a performance measure of verbal learning and memory, with medium-to-large effect sizes observed. Furthermore, the change scores from baseline to two months after completing computer training (i.e., five months later) remained significant between the two groups on the measure of verbal learning and memory.

In another randomized controlled study (Hildebrandt et al., 2007), the efficacy of a home-based computerized memory and WM training program in relapsing-remitting MS (RRMS) patients was studied. Forty-two patients were randomly assigned to an intervention or control group and underwent baseline cognitive testing. Approximately half of each group was described as being cognitively impaired upon baseline testing, defined as performance below one standard deviation of published norms on one or more neuropsychological tests. Individuals in the intervention group (*n* =17) were trained on computerized memory and WM rehabilitation tasks (developed by the researcher) for six weeks, at least five days a week for 30 minutes a day. Evaluation of treatment effects was carried out two weeks after the end of the training period. The control group (*n* = 25) received no intervention and underwent the second assessment after the same period of time as the intervention group. At the follow-up assessment, the intervention group showed better verbal learning and WM performance, as reflected by a greater reduction of individuals previously considered impaired. Of note, the patients in this study had minor cognitive impairment and the authors caution against the generalizability of the findings to MS patients with more severe cognitive impairments.

In another randomized controlled study (Vogt et al., 2009), two different schedules of a home-based computerized WM training program (BrainStim) which adapts level of difficulty to participants' performance were evaluated in 45 MS patients. Patients were assigned to 1 of 3 groups: i) high intensity training group who underwent 45 minutes of training four times per week for four weeks; ii) distributed training group who underwent 45 minutes of training twice per week for eight weeks; or iii) control group who did not receive any training. Each group consisted of 15 patients. Significant treatment effects were found in both the intervention groups, compared to the control group on measures of verbal WM. No significant differences were found between the two intervention groups.

In another interventional study with MS patients (Shatil, Metzer, Horvitz, & Miller, 2010), the impact of a home-based 12-week computerized cognitive training program which adapts level of difficulty to participants' performance (called CogniFit Personal Coach) was examined in 107 MS patients. The results of baseline cognitive testing were used for each participant in order to determine which cognitive abilities would be targeted by training. Patients were assigned to 1 of 2 groups: i) training group (n = 59) who were instructed to train three times per week for 12 weeks on a cognitive training program involving tasks identified as targets based on individual baseline cognitive performance; and ii) control group (n = 48) who were informed that they would receive the training software as a gift at the end of the study. For the training group, 24-hour technical support by phone was available; and participants who were struggling to complete training were phoned once by a study researcher who inquired about their challenges. Following training, participants in the training group showed increased performance across a number of cognitive abilities. However, the most interesting finding was that the training group showed significantly superior performance (with large effect sizes) compared to the control group in the areas of visual WM, verbal-auditory WM, and general memory. This study is one of the few which attempted to examine adherence to a home-based computerized training without prompting. Almost three-quarters of the participants in the cognitive training group used the program at home unprompted. Of the entire training group, just over one-third of the group completed all training sessions and just under two-thirds completed less than this (or none). One must be cautious when drawing conclusions from this study because training did not target WM across participants, and thus, the intervention was somewhat different depending on the needs of each participant.

In a recent functional magnetic resonance study (Sastre-Garriga et al., 2011), the authors investigated the effects of a highly specific cognitive rehabilitation program on brain activity and cognitive performance. The five week-long program consisted of computer-aided drill and practice exercises, and one non-computer-aided exercise, which targeted executive functions, attention, WM, memory, and speed of information processing. Fifteen cognitively-impaired patients with MS received rehabilitation, whereas the control group of five healthy participants received no treatment. At the end of the program, MS patients had significantly improved their performance on a measure of WM, as well as on a composite score of neuropsychological outcomes.

Attention and processing speed. Although it is common practice in rehabilitation programs to consider attention, processing speed, and memory as separate units, it can be useful to integrate a discussion of them here because impairments in any of these processes can overlap and interact in complex ways and have drastic and devastating effects on an individual's day-to-day functioning (Sohlberg & Mateer, 2001). Several studies have found gains after computer-assisted cognitive rehabilitation in adults with MS with respect to attention (Filippi et al., 2012; Plohmann, Kappos, Ammann, Thordai, & et al, 1998) and processing speed (Filippi et al., 2012; Vogt et al., 2009).

In the earliest study (Plohmann et al., 1998), efficacy of computer-based retraining of specific attention impairments was evaluated in 22 patients with MS. Patients trained for multiple periods, with each period consisting of 12 sessions over three weeks, and each session lasting 40 minutes. The four areas of attention which were trained were alertness, divided attention, selective attention, and sustained attention. Significant improvements in alertness, divided attention, and an aspect of selective attention were achieved by *specific* training for the *specific* attention impairments, and not by generalized attention training. Of note, a limitation of this study is the failure to include independent measures of attention that were not practiced in training.

In a recent randomized controlled study, Filippi and colleagues (Filippi et al., 2012) evaluated behavioural changes in 20 individuals with clinically stable RRMS through repeat administration of neuropsychological assessment. Participants assigned to the treatment group (n = 10) underwent intensive computerized cognitive rehabilitation of attention, executive functions, and information processing, for one hour, three times per week for 12 weeks. Participants assigned to the control group (n = 10) did not undergo any cognitive rehabilitation. Compared to the control group, patients in the treatment group showed significant improvement on tests of attention and information processing, as evidenced by higher scores on the former and shorter reaction times on the latter.

In an aforementioned randomized control study (Vogt et al., 2009) that investigated two different schedules of a home-based computerized WM training (high intensity vs. distributed training) in 45 MS patients, significant improvements were found in processing speed (in addition to verbal WM) in both groups. Hence, such findings suggest that this program originally designed to rehabilitate WM may transfer to remote components such as mental speed.

Neural changes. In a study described above (Filippi et al., 2012) which found significant improvement on tests of attention and information processing in MS patients who underwent intensive computerized cognitive rehabilitation, structural and functional magnetic resonance imaging techniques were also used to examine the neural substrates of cognitive changes. After 12 weeks of cognitive training, compared with the control group, the treatment group experienced an increased recruitment of several regions that were primarily located in the frontal and parietal lobes, and included the dorsolateral prefrontal cortex, anterior cingulate cortex, posterior cingulate cortex and/or precuneus, and inferior parietal lobule, during a Stroop task. Of note, these regions are all consistently recruited in cognitively demanding tasks, suggesting enhanced recruitment of brain networks following training. The authors chose to perform resting-state imaging to control for variable task performance. A significant treatment effect was found across several cognitive-related resting-state networks, which showed an increase in resting-state activity over time in the treatment group versus a decrease in resting-state fluctuations in the control group. The authors highlight the importance of this finding, stating that because healthy individuals tend to show resting-state network activity that remains stable over time, a reduction of resting-state activity within selected regions has been associated with worsening of cognitive performance over years in individuals with mild cognitive impairment (Wang, Liang, Jia, Qi, Yu, Yang et al., 2011). The finding of the current study suggests that the increased activity found at rest in individuals who underwent training might reflect the occurrence of compensatory mechanisms. Neither structural modifications to gray matter volume nor modifications to normal appearing white matter architecture were detected after training. The findings of this study are important because they suggest enhanced functional changes at the brain level, with practice, which suggests that intensive cognitive rehabilitation in individuals with MS can promote neuroplasticity.

In another study described above (Sastre-Garriga et al., 2011), which found improvements on a measure of WM and other neuropsychological outcomes in MS patients after a five-week computerized training program, the effect of the program on brain activity was also investigated, using an fMRI paradigm. MS patients had increased brain activity after cognitive rehabilitation in several cognition-related cerebellar areas when compared with healthy controls. Such findings are consistent with previous fMRI research of cognition in MS, which shows that increased brain activation may help compensate for cognitive deficits (Audoin et al., 2003; Staffen et al., 2002), via active processes of neuroplasticity possibly serving to mask the clinical and cognitive expression of brain pathology. It appears that increasing regional activation may be a strategy used by the CNS to prevent the manifestation of new deficits or to reverse those which have already manifested. Of note, cerebellar areas have been implicated in cognitive processes and though often thought of as ‘frontal deficits’, lesional studies involving the cerebellum have shown a pattern of executive dysfunction and attentional deficits produced by right-sided lesions as well as visuospatial deficits produced by left-sided lesions (Gottwald, Wilde, Mihajlovic, & Mehdorn, 2004; Riva & Giorgi, 2000). In this study, the authors concluded that their findings suggest that cognitive rehabilitation can induce increases in brain activation, thus, providing evidence to support the neuroplastic potential of rehabilitation interventions for MS patients.

In another study described above (Hildebrandt et al., 2007) which found better verbal learning and WM performance at follow-up assessment in MS patients who underwent a six-week memory and WM intervention than those who did not, authors also sought to investigate the role of brain atrophy in the degree of plasticity. The researchers found that the impact of treatment on some cognitive functions was independent from the extent of brain atrophy, whereas for other cognitive functions, individuals with a lesser degree of brain atrophy profited from the treatment. More specifically, individuals with both low and high brain atrophy profited from treatment with respect to their free recall performance on a verbal learning task. In contrast, only individuals with *low* brain atrophy profited from treatment with respect to their performance on tasks of auditory attention and motor speed (i.e., lack of changes in the high brain atrophy group but changes from pre-to-post in the low brain atrophy group). The authors suggest that a plausible explanation for the observed difference could be that free recall might involve short cortical connections, whereas other tasks might involve long-ranged connections which tend to be more vulnerable to the neuropathological effects of MS. In short, the findings of this study lend support to the capacity for neuroplasticity in the MS brain, while drawing attention to the consideration of how brain atrophy may constrain this capacity for some functions to respond to rehabilitative strategies.

Other changes. In a recent randomised, controlled multi-centre study (Mantynen et al., 2013), the effects of strategy-oriented neuropsychological rehabilitation, focusing on computer-based attention and WM retraining were examined in 98 patients with MS. Patients were assigned to 1 of 2 groups: i) intervention group who also received outpatient neuropsychological rehabilitation, once a week in 60-minute sessions for 13 consecutive weeks (n = 58); or ii) control group who did not receive any rehabilitation (n = 40). While training had no significant effect on cognitive test performance, it was found to have a positive effect on perceived cognitive deficits. The intervention group perceived significantly fewer deficits than the control group, both immediately after completing the intervention and at six-month follow-up. Furthermore, patients in the intervention group were able to meet the personal goals they set for the rehabilitation.

In a study described earlier (Plohmann et al., 1998), participants who completed cognitive training were also administered a self-rating inventory assessing everyday attentional problems. Analysis of the responses revealed less distractibility and fatigue as well as less slowing of mental processes and physical activities, following cognitive training. Furthermore, via an exit interview many of the patients acknowledged the importance of the experience of improving cognitive performance for their own sense of self-esteem, especially with respect to a progressive disease.

In another study described earlier (Vogt et al., 2009), the effects of cognitive training on fatigue were assessed with two different self-reports before and after training. Almost all the participants who underwent training were considered to have clinically relevant fatigue (as evidenced by elevated scores on both questionnaires). One of the most notable results of the study was the significant decrease in self-reported fatigue in patients who completed training, compared with those who did not undergo training. Of note, no effects were found on quality of life or depression. This study's researchers reported a high compliance rate in their study (i.e., nearly 100% of individuals finished all 16 training sessions in the allocated time) and attributed this to a number of features of the program: the computer game-like nature of the program and its use of three different modules of activities helps to maintain interest and prevent training from becoming repetitive; the ability of the program to automatically adapt level of difficulty for each patient helps to maintain appropriate challenge for the patient; and the home-based nature of the program increases flexibility and allows individuals to train around their own schedules.

Taken together, findings from the adult rehabilitation literature suggest that: i) MS patients can tolerate, adhere to and complete an intensive, computerized cognitive training program; ii) home-based programs may help to increase compliance because individuals can flexibly train around their own schedule; iii) similarly, the adaptive nature of such programs may help to increase compliance as well as generate positive experiences with training by providing an appropriate level of challenge for participants; iv) gains in both visual and verbal WM have been observed, together with gains in attention and processing speed, as a result of cognitive training; moreover, MS patients appear to report positive effects on their own sense of self-esteem, perception of cognitive deficits, and fatigue as a result of cognitive training; v) changes at the neural level have been observed in MS patients after cognitive training, such as increased brain activation, which serves to promote neuroplasticity. With respect to this last point, the research highlights how important it is to consider that the extent of brain injury/atrophy may influence the capacity for neuroplasticity for some cognitive functions. Accordingly, the following section will review some important principles of neuroplasticity which need to be considered in order to understand the mechanisms underlying changes seen after cognitive training.

Section 6: Neuroplasticity

When considering cognitive rehabilitation, an important distinction to make is whether the focus of rehabilitative efforts is on *compensation* or *restitution*. Compensation refers to the use of strategies and/or external aids in order to circumvent cognitive dysfunction and allow a person to successfully carry out a task. In contrast, the goal of restitution is to reorganize underlying neural circuitry and attempt to *improve* damaged cognitive functions (Sohlberg & Mateer, 2001). A critical concept that is related to the latter method (restitution) is *neuroplasticity*. Neuroplasticity refers to the brain's ability to change and alter its structure and function. Within the CNS, neuroplasticity is sustained by a variety of changes in grey matter (e.g., changes in neural morphology), white matter (e.g., changes in axonal branching, myelination), as well as other tissue compartments (e.g., glial cell size and number) (Zatorre, Fields, & Johansen-Berg, 2012). Though there are various mechanisms which underlie neuroplasticity after brain injury and which have significant implications for rehabilitation, the one that is most relevant to computerized cognitive training and which will be reviewed here is *modification of synaptic connectivity* (Sohlberg & Mateer, 2001). This process refers to the phenomenon whereby following brain injury, neurons that have lost input from a damaged neuron develop new dendrites to receive information from another neuron either in the same circuit or from another circuit further away. Such synaptic plasticity is ongoing and is in the process that underlies associative learning as well as experience-dependent learning. That is to say, if there were no inputs to drive the system, such new connections would not be able to form. A critical implication of this concept with respect to rehabilitation is that differences in an individual's experience following injury will inevitably shape synaptic interconnections, which in turn, will influence one's recovery (Robertson & Murre, 1999a).

Hebbian learning is an important concept that helps to understand the neural basis of behaviour. Popularly referred to as the "cells that fire together, wire together" phenomenon, Hebb (Hebb, 1949) argued that synaptic connections are strengthened when two neurons or groups of neurons that have been disconnected by a lesion become reconnected if they are activated at the same time. Moreover, it is through several repetitions of such simultaneous activation that the two disconnected neurons (or groups of neurons) become reconnected. There is plenty of evidence to support this phenomenon, including intracortical microstimulation research, whereby electrically stimulating cortical cells to fire in temporal proximity has been shown to strengthen synaptic connections between them (Dinse, Recanzone, & Merzenich, 1993).

Guided recovery. There is evidence to suggest that a triage of recovery patterns after brain injury exists: some individuals appear to recover spontaneously; some show very little or incomplete recovery even over several years; and some show recovery, but this recovery seems to depend on rehabilitative input (Robertson & Murre, 1999b). It is this third group that is referred to as the 'guided recovery' group and for which the focus is on restitution-oriented rehabilitation, in particular, Hebbian learning-based reconnection. Facilitating recovery among damaged neural networks appears to benefit from additional external structured input (Robertson & Murre, 1999b). For example, one study (Mayer, Brown, Dunnett, & Robbins, 1992) showed that rats given striatal neural transplants only benefited from transplants when they were provided with the opportunity for perceptuomotor learning. That is, in the absence of behavioural driving of the neural tissue, sufficient connectivity did not develop to produce behavioural improvements. In another animal study (Nudo, Wise, SiFuentes, & Milliken, 1996), researchers found that following lesions to the hand area in monkeys, hand movement representations in originally undamaged areas adjacent to the lesion were lost. However, intensive behavioural training of skilled hand use prevented this loss of representation in adjacent tissue, and actually led to larger areas of hand representation. Taken together, these findings suggest that structured input and structured activity (i.e., rehabilitative training) can guide synaptic reorganization, resulting in behavioural improvements.

Research suggests that wherever possible, stimulation should be *targeted* to foster *adaptive* connections within a lesioned network and to minimize the possibility of fostering faulty or maladaptive connections (Robertson & Murre, 1999b). In a physiotherapy study of motor rehabilitation in humans (Bütefisch, Hummelsheim, Denzler, & Mauritz, 1995), highly repetitive hand and finger movements in the impaired arm produced significantly greater improvement in function than standard hand and finger exercises which involved a range of movements. This concept is critical to understanding the mechanisms underlying behavioural change in targeted computerized training programs.

Neuroplasticity in MS. Despite the widespread and multifaceted nature of the disease, there is evidence to show that functional reorganization accompanying recovery across brain systems in MS can limit the impact of damage on behaviour (Filippi et al., 2012; Reddy et al., 2002; Tomassini et al., 2012a). Functional studies which have investigated working memory

(Chiaravalloti et al., 2005) and other executive functions (Mainero et al., 2004) in MS have consistently found that these processes involve activity of wider and more bilateral networks of task-specific regions in MS patients than in healthy controls. Stronger interhemispheric functional and structural interactions have been observed in MS patients than in controls, with such increased strength of connectivity found to be associated with damage to specific, task-relevant white matter tracts (Rocca et al., 2009). In a recent review of neuroplasticity and functional recovery in MS (Tomassini et al., 2012b), the authors describe a number of individual-specific and disease-related factors which could influence adaptive functional reorganization in MS. Age at disease onset may influence the premorbid cognitive functional reserve, which may in turn, help explain the effect of age on cortical reorganization processes that underlie recovery in MS. The type, location, extent, and severity of MS damage affects adaptive reorganization. For example, acute inflammation (e.g., such as in RRMS) alters functional brain responses, which then return to baseline activity with resolution of inflammation, whereas chronic inflammation (e.g., primary progressive MS) may produce sustained reorganization of function across brain systems, that may either be adaptive or maladaptive. Furthermore, more extensive and irreversible tissue loss is usually associated with reduced potential for functional reorganization. The authors argue that a substantial preservation of brain structural architecture via efforts aimed at promoting functional reorganization in MS can enable underlying neural mechanisms to act, even when MS damage or task demands are increased. Finally, the authors describe the importance of using optimal methods that can detect the effects of interventions on promoting functional reorganization. fMRI has been widely used in studies on recovery in MS, to detect changes in baseline neural activity and vascular response as a result of interventions (Hyder, Rothman & Shulman, 2002). The authors of the review article highlight the importance of controlling for individual and disease-related factors that may modulate neural responses in order to optimize interpretability of the results.

The next section will describe a popular computerized WM training program (Cogmed) that has been used with a number of pediatric and adult-based populations, but has yet to be implemented in patients with MS.

Section 7: Cogmed Training

The Cogmed program was developed in the early 90's by a Swedish neuroscience researcher, Torkel Klingberg, whose pioneering research demonstrated that WM capacity could be increased through training. The program is based on the tenet that WM is a core cognitive function which is known to be related to several other cognitive functions and skills, including reasoning, attention, reading, and mathematical ability (Dumontheil & Klingberg, 2012; Gathercole & Pickering, 2000; Geary et al., 2004; Swanson, Ashbaker, & Lee, 1996). While previously the capacity of an individual's WM was thought to be limited – primarily constrained by the amount of information one can keep in mind at a given time – there has been a wave of research studies in recent years, claiming that WM capacity may be increased by intensive training using computerized WM tasks (Klingberg, Forssberg, & Westerberg, 2002; Klingberg et al., 2005; Klingberg, 2010b). The design of the Cogmed program was purportedly inspired by previous research studies which had been successful in enhancing sensory discrimination and demonstrating cortical plasticity in sensory and motor cortices. Support for the idea that WM could be increased using nonpharmacological approaches came from a seminal study in which macaque monkeys showed changes in neural activity in the principal sulcus and prefrontal cortex after having trained on a WM task for several weeks (Rainer & Miller, 2000). It is from studies such as this that Klingberg gleaned important principles for the development of the Cogmed program, such as intensity and duration of training.

As noted earlier, simple Hebbian learning has been suggested as a possible mechanism that can explain how repeated activation (i.e., training) can improve WM capacity via strengthening the synaptic connectivity between neurons within the WM network (Klingberg, 2011). That is, the effect of WM training has been likened to the plastic effect of skill learning (Westerberg & Klingberg, 2007). Over the course of many repetitions of the same or substantially similar episodes of information processing, synaptic changes occur among connections in neocortical systems. When there is an accumulation of such changes, a neuronal network underlying a particular cognitive skill may be strengthened (McClelland, McNaughton, & O'Reilly, 1995). The work by Klingberg and his colleagues is groundbreaking, albeit based on existing knowledge from the field of neuroscience suggesting that the brain is plastic. Another key aspect of the Cogmed training program is that it uses an adaptive training algorithm which presents individuals with exercises of increasing difficulty (both span length and complexity) at a level which is slightly greater than that which they have recently reached successfully (Kronenberger et al., 2011). The following section will provide a brief discussion of existing research which has attempted to describe how feasible Cogmed is to implement and what the experiences are of those who complete training.

Feasibility and subjective experience of Cogmed training. When considering whether or not to implement an intervention, studying the feasibility of an intervention can produce results that help to determine whether it should be recommended for large-scale efficacy testing (Bowen et al., 2009). Feasibility research can be used as a determinant for accepting or discarding an intervention, in order to advance only those interventions that appear to merit testing (i.e., have a high probability of efficacy). Furthermore, examining feasibility can help to identify whether any research methods and/or protocols require modification. Exploring feasibility encompasses considering things such as how the intended individual recipients react to an intervention, and the practicality of delivering an intervention (i.e., taking into account constraints on time, resources, and commitment) (Bowen et al., 2009).

A handful of recent studies with clinical populations have aimed to describe the feasibility and acceptability of Cogmed by those who undergo the training program (Hardy, Willard, Allen, & Bonner, 2013; Kronenberger et al., 2011). In a recent pilot study (Kronenberger et al., 2011), the authors aimed to evaluate whether Cogmed was feasible and accepted by nine deaf children with cochlear implants and their parents. Parent ratings were evaluated with the *Program Feasibility Questionnaire*, a 15-item measure designed to assess challenges, problems, and satisfaction with the training program. Results from the questionnaires indicated that half of the families assessed were satisfied with the program, two-thirds said that they would recommend the program to others, and nearly half agreed with statements indicating that they saw improvements in their child's attention and WM. About three-quarters of parents indicated that the program took a significant amount of effort from the parent and child, particularly during the final week of training. The authors concluded that Cogmed is appropriate and acceptable for children with cochlear implants, however, high levels of motivation and effort are necessary for the program's implementation.

In a recent randomized pilot study (Hardy et al., 2013), the authors aimed to examine the feasibility of Cogmed in 20 survivors of pediatric cancer, including compliance. Participants were randomized to either the regular, adaptive version of Cogmed (*n* = 13) or a non-adaptive, active control condition (*n* = 7). The authors developed a 13-item survey to assess technical feasibility, ease-of use, satisfaction, and compliance. The survey was administered to participants and parents after all Cogmed training had been completed. The definition of compliance used in this study was based on previous reports (Klingberg et al., 2002; Klingberg et al., 2005), which define compliance as completion of at least 80% (20 sessions) of the required sessions. In terms of technical feasibility, parents reported few problems with the technical use of the computer program, and 100% of families reported that the program was easy to log into and to navigate through the activities. Half of parents of children in both the adaptive and non-adaptive groups reported that their children either 'often' or 'always' enjoyed completing training sessions. Satisfaction with the training program was high in parents of children in both groups, with two-thirds of parents rating themselves as 'very' satisfied with their child's training experience. One-fourth of the participants in the adaptive group reported feeling 'often' frustrated while completing the exercises, and one-third of the participants in the non-adaptive group reported feeling frequent boredom. In terms of compliance, 85% of all participants were considered compliant, and 75% completed all training sessions.

In a study designed to examine whether younger adults with moderate to severe cognitive deficits after brain injury can benefit from Cogmed training (Johansson & Tornmalm, 2011), the authors also sought to find out if training has any impact on daily life activities. Eighteen individuals with acquired brain injury (ABI) and WM deficits underwent Cogmed training. Semi-structured exit interviews were conducted with all participants in order to investigate their subjective experiences of changes in daily life functioning. Qualitative analysis of the interview data generated three main themes: self-awareness, improvement, and general effects. With respect to self-awareness, most participants provided examples of increased understanding that WM dysfunction was causing many of their breakdowns in daily life. In terms of improvement, several participants reported increases in their ability to find their way and self-confidence in remembering where they were, how they arrived there, and how to return home. Regarding general effects, though most participants acknowledged that the training was mentally exhausting, all participants acknowledged that they would still recommend the program to others in their situation.

Taken together, these findings suggest that Cogmed can be feasibly implemented with high levels of compliance, and that it appears to be well tolerated by various clinical populations. In terms of experiences with training, the findings are somewhat equivocal but seem to suggest that Cogmed is user-friendly and enjoyable in up to two-thirds of participants, and it can provide individuals with more insight about their functioning. Findings suggest that the training program requires considerable effort and time to complete, and that it is important to consider mental fatigue. Research on the effects of Cogmed will be reviewed in greater detail in the next section.

Efficacy of Cogmed training. There is a large body of research demonstrating both near and far transfer effects of computerized training using the Cogmed program. Near-transfer effects refer to effects on tasks which resemble those trained on (e.g., improvements on a neuropsychological test assessing visuospatial WM following training on a computerized visuospatial WM task), whereas far-transfer effects refer to effects on tasks that are different from those trained on (e.g., improvements on a neuropsychological test of mathematical ability following training on WM tasks (Melby-Lervåg & Hulme, 2013). While evidence for near transfer effects of Cogmed training to untrained WM tasks appears largely supported, evidence of far transfer effects to other functions that rely upon WM (including attention, complex reasoning, response inhibition, fluid intelligence, initiation, and planning/organization (Beck, Hanson, Puffenberger, Benninger, & Benninger, 2010; Jaeggi, Buschkuehl, Jonides, & Perrig, 2008; Klingberg et al., 2002; Klingberg et al., 2005; Olesen, Westerberg, & Klingberg, 2004; Westerberg et al., 2007), is somewhat mixed at present and has been met with controversy within recent years (Jaeggi, Buschkuehl, Jonides, & Shah, 2012; Shipstead, Hicks, & Engle, 2012). In response to the controversy, other researchers (Jaeggi et al., 2012) argue that a main reason for mixed findings across studies is because the studies are very heterogeneous and include a wide variety of populations. In a recent attempt to tackle this problem, a recent systematic meta-analytic review of computerized WM training programs across studies was undertaken (Melby-Lervåg & Hulme, 2013). To be included in the review, studies had to be: either randomized controlled trials or quasi-experiments with a treatment and either a treated or untreated control group tested pre- and post-test; and the treatment group had to receive an intervention for at least two weeks based on an adaptive computerized program designed to train WM. Thirty different WM training studies were included, eight of which were studies using Cogmed. The meta-analysis revealed immediate gains on measures of visual-spatial and verbal WM (moderately- and largely-sized, respectively), and together, these results were highly significant (i.e., $p < .001$). Interestingly, the results of the analysis also showed that the type of training performed is important and that the intervention program used was found to be the only significant moderator of training effects. More importantly, out of the five programs included in the review (i.e., Cogmed, Jungle Memory, N-back training, Cognifit, Other [research-based programs]), Cogmed was found to produce the largest effect sizes for both immediate visual-spatial and verbal WM. The authors of the meta-analysis concluded that there was no evidence of generalization of WM training to other skills (nonverbal, verbal ability; inhibition; word decoding; arithmetic). Similar conclusions were drawn in another preceding review (Shipstead et al., 2012).

Another recurring topic of controversy in the field is the question of whether Cogmed training produces long-term effects on WM, and if so, for how long. The meta-analysis described above (Melby-Lervåg & Hulme, 2013) revealed that several studies of Cogmed with a follow-up duration from 3 – 6 months have shown that effects persist. While the meta-analysis suggested significant sustained effects on visual-spatial WM with a moderate effect size and high significance, the authors acknowledged the need for more research in this area. In another more recent review (Shinaver, Entwistle, & Söderqvist, 2014), the authors argue *for* the presence of long-term effects of Cogmed training, using the following argument: they suggest that since WM is highly taxed in day-to-day functions, particularly in school settings, improved WM capacity immediately following WM training could enable children to participate in educational activities at a more advanced level than prior to training. Hence, this new type of cognitive "engagement" that children experience could allow for more frequent "natural" opportunities to challenge one's WM capacity, which could in turn, promote a continuation of such WM expansion long after WM training has been completed. The authors are quick to acknowledge that their theory should be viewed as speculation until further research is conducted. They aptly highlight the risk of drawing any strong conclusions, arguing against the efficacy of Cogmed, until further research can shed more light.

In response to critics of Cogmed studies, another group of researchers (Morrison & Chein, 2012) argue that there are still many fundamental questions to be answered in order to maximize the impact and value of Cogmed. They suggest that future Cogmed research studies should strive to address questions including: i) what conditions are needed for positive transfer of training; ii) which individual characteristics moderate receptivity to training; and iii) which specific cognitive mechanisms are targeted by training. The authors suggest a movement toward new studies that address the current gaps in methodology.

Using Cogmed, gains in WM capacity have been shown in pediatric conditions, including attention deficit hyperactivity disorder (ADHD) (Beck et al., 2010; Klingberg et al., 2002; Klingberg et al., 2005); prematurity (Løhaugen et al., 2011), pediatric cancer (Hardy et al., 2013), hearing impairment (Kronenberger et al., 2011), as well as in younger adults with stroke (Westerberg et al., 2007) and acquired brain injury (Johansson & Tornmalm, 2011; Lundqvist, Grundström, Samuelsson, & Rönnberg, 2010). Details describing the efficacy of Cogmed in pediatric populations, as well as, younger adult populations (given that the current study sample included young adults up to the age of 24), will be presented in the next section.

Efficacy of Cogmed in pediatric populations. In one of the earliest Cogmed research studies (Klingberg et al., 2002), the authors investigated whether WM capacity could be improved by cognitive training in 14 individuals with ADHD who also had WM deficits. Using a double blind, placebo controlled design, half of the participants (*n* =7) were assigned to the treatment group and the other half (*n* =7) were assigned to a control 'placebo' group. Individuals in both groups undertook training of a visuo-spatial WM task and a spatial-verbal WM task, 4-6 days a week, for at least 5 weeks. However, the program administered to the placebo group did not include two features: the difficulty level was not interactively adjusted, and daily training amounted to less than 10 minutes per day. When test-retest changes in the treatment group were compared to test-retest changes in the placebo group, there was a significant treatment effect for the practiced visuo-spatial WM task [pre-treatment *M (SEM)* = 4.71 (0.21), post-treatment *M*

(SEM) = 6.43 (0.41)] as well as for a non-practiced visuo-spatial WM task [pre-treatment *M (SEM)* = 4.36 (0.12), post-treatment *M (SEM)* = 6.32 (0.25)]. Effect sizes were not reported. In terms of far-transfer effects, the authors also found significant improvement in the treatment group and significant group difference on a measure of nonverbal complex reasoning and on another measure of response inhibition. In addition, motor activity was found to be significantly reduced in the treatment group following training.

The results of the study described above (Klingberg et al., 2002) were replicated and expanded in a randomized controlled trial with 53 individuals who were identified as having ADHD (Klingberg et al., 2005). Similar to the protocol used in the previous study (Klingberg et al., 2002), participants were randomly assigned either to a treatment group or a placebo group, and underwent 25 training sessions over 5-6 weeks. Consistent with the findings of the earlier study (Klingberg et al., 2002), the authors found significant improvements of the treatment group on non-practiced measures of visuo-spatial WM, nonverbal reasoning, and response inhibition; effect sizes were 0.93, 0.45, and 0.34, respectively. In contrast to the earlier study (Klingberg et al., 2002), the authors did not find significant improvements on motor activity. Moreover, this study found significant improvements on parent-reported symptoms of inattention and hyperactivity post-training.

In a randomized pilot study described earlier (Hardy et al., 2013), a secondary aim was to examine the preliminary efficacy of Cogmed in 20 survivors of pediatric cancer. Deficits in WM have been proposed to underlie the changes seen in intelligence and academic performance which are frequently observed in pediatric cancer survivors. Participants were randomized to either the regular, adaptive version of Cogmed (n = 13) or a non-adaptive, active control condition (n = 7) which is identical to the other version except that the level of difficulty never increases. When controlling for estimated IQ and baseline performance, scores on a non-trained task of visual WM for the adaptive group increased significantly compared with the non-adaptive group, with a large effect size of $d = 0.94$. Furthermore, over one third of participants in the adaptive group exceeded the reliable change index (RCI) threshold for the visual WM measure compared with none of the participants in the non-adaptive group. No differences in verbal WM were observed between groups. In terms of far transfer effects, participants in the adaptive group demonstrated greater improvement over those in the non-adaptive group on parent-rated learning problems ($d = 0.80$). Finally, this study also found that baseline estimated IQ scores were moderately correlated with the magnitude of change in performance-based outcomes following training (i.e., individuals with higher baseline IQ scores tended to show greater improvements in visual WM following training).

In another pilot feasibility study described earlier (Kronenberger et al., 2011), a secondary aim was to investigate the preliminary efficacy of Cogmed in a sample of 9 children (aged 7 – 15 years) with WM deficits who use cochlear implants. Following training with Cogmed, participants showed improvement on all trained Cogmed exercises (with the exception of one exercise on which participants only receive five days of training). More specifically, participants showed a performance improvement value of 0.70 or higher on exercises. Importantly, scores improved significantly on untrained measures of verbal and visual WM, as well as parent-reported WM, with standardized change values showing average improvement of about one-half *SD* or more over pre-training values. Far transfer effects were also observed, as evidenced by the significant improvement in sentence-repetition raw scores (with an increase of 0.69 *SD*) over the pre-training value.

Efficacy of Cogmed in younger adults. In a randomized control study (Lundqvist et al., 2010), the effects of Cogmed training were examined in adult patients suffering from WM impairments after acquired brain injury (ABI). A secondary objective of this study was to examine the effect of Cogmed training on patients' ratings of their quality-of-life and health. In order to control for test-re-test effects and to ensure that outcome was from training and not spontaneous improvement, twenty-one participants with ABI were randomized into two groups at baseline: group one (n =10) who underwent Cogmed training for five weeks, and group two (n = 11) who did not receive any training during the same period but underwent Cogmed training at a later date. Results revealed that individuals in both groups showed statistically significant gains on trained Cogmed exercises, as evidenced by comparing their baseline performance to the highest performance achieved during the training period, irrespective of when they received training. The effect size was large, at 0.95. When examining performance on untrained measures of both visual-spatial and verbal WM across all 21 individuals, significant increases on measures were found from baseline to four weeks post-training (*NB.* Effect sizes not reported). Though self-rated quality of life did not change from baseline to immediately post-training, self-rated overall health increased 20 weeks after training, which suggests a training effect on cognitive functioning in day-to-day living. Importantly, the results showed that training effects were not due to re-testing or from change over time due to other factors.

In a randomized pilot study (Westerberg et al., 2007), the effects of Cogmed training were examined in 18 individuals who had suffered a stroke 1-3 years earlier. Participants were randomized to one of two conditions: either the treatment group (underwent Cogmed training) or a control group who did not engage in any training. Following training with Cogmed, the training group showed a significant increase in comparison to the control group on WM tests which resemble the Cogmed exercises (i.e., Digit span, Span board). More interestingly, the greatest treatment effect was found on an untrained test of WM and attention. No treatment effects were found on measures of nonverbal reasoning, response inhibition, or declarative memory.

Taken together, the studies described provide preliminary evidence for improved performance in pediatric and young adult clinical populations on both visual and verbal WM tasks which are dissimilar to those trained on (i.e., untrained tasks of WM). This suggests that cognitive training can actually increase WM capacity and/or general WM skills rather than simply facilitate the development of task-specific strategies (Klingberg, 2010b).

Section 8: Motivation and Response to Rehabilitation

When designing rehabilitative interventions, it is important to understand how variables which are separate from the actual treatment (e.g., personality characteristics, fatigue level) may influence one's response to a treatment. Such knowledge is critical for identifying subgroups of individuals who may show greater or lesser benefit from rehabilitation. One way to examine the issue is to consider what is different about the patients and their subjective experience with the intervention for those who show a positive versus a poor response to an intervention (Medalia & Richardson, 2005). A delineation of such factors can help to elucidate the mechanisms of a positive treatment response. This information, in turn, is important for making scientific hypotheses and clinical decisions about how to improve rehabilitation programming and how to enhance rehabilitation outcome.

Though there is a great need for considering individual characteristics of participants who undergo cognitive rehabilitation, current knowledge in this area is very limited. Age and illness severity emerged as important factors in one cognitive rehabilitation study (Shatil et al., 2010) (described earlier in section 5). When comparing those who completed the entire cognitive training program to those who did not, the only difference that emerged was that completers were older than non-completers (mean = 49.9, 40.1 years, respectively). Furthermore, this study revealed a positive correlation between age and illness severity, such that the older the participants were, the more severe their illness. Putting these two findings together, it was hypothesized that younger participants may have left the training group because they did not feel the urgency for cognitive training. Such findings seem to suggest that older participants, for whom the illness is more severe, may be more motivated to complete cognitive rehabilitation and thus, more likely to complete training. More generally, these findings highlight the importance of assessing a potential candidate's own perceived need for and interest in cognitive rehabilitation, as this may influence adherence.

There is some evidence to suggest that IQ can influence the degree to which participants benefit from cognitive rehabilitation (Hardy et al., 2013). In this study, baseline estimated IQ scores were found to be moderately correlated with the magnitude of change in performance-based outcomes following training (i.e., individuals with higher baseline IQ scores tended to show greater improvements on a visual WM task following training).

The importance of paying attention to motivational factors that can affect a participant's expectations and coping strategies during a rehabilitation program has been previously emphasized (Grahn, Ekdahl, & Borquist, 2000; Grahn & Gard, 2008). 'Motivation' may be defined as everything that drives and sustains human behavior (Steers & Porter, 1991). It is the process that provides an individual with its energy and direction (Reeve, 1997). Motivation is regarded as a biopsychosocial phenomenon in the sense that it incorporates biology, cognitions, and emotions (Smith, 1993). According to Maslow's hierarchy of needs (Maslow, 1987), basic needs lower down in the hierarchy (i.e., biological needs, need to belong) must be satisfied before the higher growth needs can direct behaviour. Cognitions, as they pertain to motivation, include goal-setting (Reeve, 1997). Goals are what energize behaviour and guide an individual's planning and attention. Emotions also serve as motives to energize and direct behaviour (Reeve, 1997) because they are subjective feelings that make a person feel a certain way in a specific situation, and help prepare the body to cope effectively with situations. Motivation in a rehabilitation setting may be affected by a combination of individual factors (i.e., clients' interests, attitudes, expectations, self-confidence) and social factors (i.e., level of social support; Gard, 2001). 'Motivation for change' may be defined as a summary of all the motivating factors that stimulate an individual to make changes in his/her life situation (Gard, Rivano, & Grahn, 2005). Furthermore, motivation for change has been shown to be important for positive rehabilitation outcomes (Gard & Sandberg, 1998; Gard, 2001; Grahn et al., 2000). Thus, a detailed analysis of an individual's motivation for change may help to better understand his/her particular response to cognitive rehabilitation.

As part of an initiative to increase return to work for patients listed as sick with chronic musculoskeletal pain, patients' motivating factors for return to work were investigated (Gard & Sandberg, 1998). Ten patients (who all worked in the health sector) participated in a rehabilitation program over 12 weeks which focused on pain reduction, identifying and finding solutions to pain problems in actual life and work situations, and training of functional capacities needed in work and life situations. Results suggested that self-confidence was an important factor for return to work, together with relationships, in terms of being able to cooperate with colleagues and provide services to clients. These findings are consistent with previous research which has shown that people's self-confidence and self-beliefs of efficacy may affect their level of work motivation (Bandura & Cervone, 1986). Self- beliefs of efficacy may also affect thought patterns that may be helpful or hindering as well as the level of goals that a person establishes (Gard & Sandberg, 1998).

As discussed previously, the research to-date supporting the effectiveness of WM training may show some mixed results across and within studies because individual differences (e.g., age, personality or pre-existing abilities) have not been taken into consideration. One particular characteristic which could play an important role in cognitive training outcomes is the degree to which participants are intrinsically vs. extrinsically motivated to participate (Jaeggi, Buschkuehl, Shah, & Jonides, 2013). In a recent noteworthy randomised controlled study (Jaeggi et al., 2013), the authors aimed to describe how motivation may serve as a moderator of transfer effects and provide a possible explanation for differential results across cognitive training studies. Seventy-eight individuals were randomly assigned to one of two WM interventions: i) adaptive single *n*-back task; or ii) adaptive dual *n*-back task in which an auditory *n*-back task was combined with a visuospatial task; or an active control group, which required participants to answer vocabulary, science social science, and trivia questions. This condition was also adaptive, so that new items replaced items that were successfully learned. In addition to the participants in these conditions, 34 other participants were recruited to take part in baseline measurement sessions only, and they did not complete any training. Results suggested that participants who agreed to participate in the training study (i.e., one of the three adaptive conditions) reported more cognitive failures at baseline assessment than those who completed just the baseline measurement, without the intention to train. Interestingly, the participants who reported cognitive failures did *not* perform worse on the baseline tests administered. The participants with the highest pre-test scores combined with the highest need-for-cognition scores were the ones who actually completed the training program. The authors concluded that a combination of high intelligence paired with self-perceived cognitive dysfunction and an increased need for cognition seems to make up the type of person who is motivated for change to their life situation and thus, motivated to complete a training study. Such a combination of characteristics also seems to describe a person who is more intrinsically motivated (e.g., driven by the sole possibility of improving their well-being) rather than extrinsically motivated (e.g., driven by monetary rewards). These findings are consistent with the results of the other aforementioned studies (Hardy et al., 2013; Shatil et al., 2010). Another related combination of personality characteristics that may be related to persistence to engage with a program that may not always be enjoyable and interesting is a trait that has been coined "grit" (Duckworth, Peterson, Matthews, & Kelly, 2007). "Grit" is defined by the authors as perseverance and passion for long-term goals.

Taken together, these findings highlight the importance of taking clinical and demographic characteristics (i.e., age, illness severity, IQ) as well as motivation into consideration when evaluating an individual's response to cognitive training. Furthermore, a delineation of specific components of motivation (i.e., motivation for change in one's life situation, intrinsically versus extrinsically motivated) may shed light on differential training outcomes across participants which may result within a study. In turn, such valuable information may serve as a way of identifying ideal candidates for cognitive rehabilitation who are likely to not only adhere to and successfully complete a training program, but to *benefit* from training.

Chapter Two: Aims and Hypotheses

Primary Aims:

1) To establish the feasibility of implementing Cogmed in patients with pediatric-onset MS who have cognitive dysfunction. This open pilot study specifically assessed treatment feasibility, including adherence and training tolerance by participants.
2) To describe the qualitative experiences of pediatric-onset MS patients completing computerized cognitive training.
3) To explore how individual characteristics and the qualitative experiences of participants may contribute to overall outcome with the training program.

Supplementary Aims:

1)To explore how the performance of pediatric-onset MS patients, who have cognitive dysfunction, on computerized WM tasks changes over the course of training.
2) To provide preliminary evidence for the efficacy of a computerized WM intervention program (Cogmed RM) on targeted cognitive abilities in a sample of at-risk pediatric-onset MS patients.
3) To use the information gathered from aims one through five to develop recommendations for the implementation of a cognitive rehabilitation program in pediatric-onset patients.

Hypotheses

1) Based on prior rehabilitation studies conducted in adults with MS and other pediatric neurologic populations, pediatric-onset MS patients will adhere to, tolerate well and complete an intensive home-based computerized WM training program (Cogmed).

2) Individuals who report positive subjective experiences with the Cogmed training program will be more likely to show better adherence and tolerance, as well as improved outcomes from baseline, as assessed by subjective and/or objective measures of cognitive performance.

3) Individuals who express higher levels of motivation for change will be more likely to show better adherence and tolerance, as well as, improved outcomes post-intervention.

4) Based on prior Cogmed studies conducted in other neurologic populations, pediatric-onset MS patients will show improved WM performance on trained and non-trained tasks, but no improvement on non-WM tasks

Chapter Three: Methods

Study Design

An exploratory mixed methods design with a concurrent triangulation strategy (Creswell, 2003) was employed in the current study to investigate the feasibility and acceptability of implementing a WM training program for individuals with pediatric-onset MS. A baseline neuropsychological screening assessment was conducted for all eligible patients and computerized training commenced one week following the pre-training (baseline) assessment. A repeat neuropsychological assessment and semi-structured exit interview were performed one week after the intervention was completed. Quantitative data included summary statistics, Cogmed-specific training outcomes, ratings on weekly questionnaires, and performance on pre- and post-training neuropsychological assessment measures. Qualitative data included information about participants' experiences with the Cogmed program which was obtained from exit interviews. Quantitative data were subsequently triangulated with qualitative data in order to investigate the 'convergence' of both the data and the conclusions derived from them (Denzin, 1994).

Participants and Recruitment

Patients who were diagnosed with clinically definite relapsing-remitting MS prior to the age of 19, were between the ages of 14 and 24 at baseline evaluation, and who were deemed possible candidates for the present study, were referred by neurologists and clinicians in the community who were made known of the study. Patients included individuals who are currently or were previously undergoing care at the Pediatric MS Clinic within SickKids Hospital, and patients participating in an fMRI study at York University who were either recruited from SickKids Hospital or the community via an advertisement that was placed on the MS Society website. Patients were selected according to the following <u>inclusion criteria</u>: i) stable phase of the disease for at least three months before inclusion (i.e. no relapse confirmed by neurologist during this period); ii) no corticosteroid treatment in the four weeks before inclusion; and iii) performance on baseline cognitive testing falling at least one standard deviation below the normative mean on at least one measure of attention or verbal learning, and/or reported subjective complaints of cognitive deficits on the Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ)[2] (Benedict et al., 2003). Exclusion criteria were: i) history of cerebral trauma; ii) current psychiatric illness; iii) illicit drug or alcohol misuse; iv) non-fluent in English; v) visual disturbance or severe motor disorder of the arms that would interfere with completing the computerized training; and vi) IQ below 70. From an initial pool of 45 patients (14-24 years of age), 17 patients were identified as meeting inclusion criteria and being eligible for recruitment. All of these individuals were sent a letter introducing the study, explaining its rationale, and inviting them to participate. Follow-up phone calls were then made and a brief telephone screen was conducted two weeks after the letters had been distributed. If inclusion criteria were met, and patients agreed to participate, an appointment was scheduled at York University for baseline cognitive testing and orientation to the cognitive training program. The study was approved by the ethical committees of The Hospital for Sick Children and York University, Toronto. Recruitment outcomes are reported in the results section.

Clinical Characteristics of Sample

Regarding clinical features of the MS group (n = 9), the mean age of disease onset was 14.3 years (SD = 3.3, range = 7.6-18.5). The mean disease duration was 4.5 years (SD = 3.1, range = 0.9-10.3). The total number of relapses documented in the patient health records ranged from 1-

[2] For one participant (COG_05), the MSNQ was not completed. Instead, data from the cognitive subscale of the PedsQL Multidimensional Fatigue Scale [Young Adult Report (ages 18-25) was used (Varni, Seid, & Rode, 1999).

13 with a median score of 3.5 relapses. Number of relapses was not available for one of the participants and is based on eight individuals. The Expanded Disability Status Scale (EDSS) score was obtained from the patient's medical chart using data from the clinic visit that was closest in time to the patient's baseline assessment. EDSS scores were recorded on average within 7.8 months (SD = 9.9 months) of the baseline assessment. The majority of patients (6/9) had a low grade of physical disability as characterized by an EDSS score below 3 (*Mdn* = 1.5, range: 1.0-5.0). None of the patients required ambulatory aid and all had normal functioning in the right upper limb. Seven of the 9 patients (78%) were receiving disease-modifying treatment at time of evaluation. Treatments included: Avonex (n=2), Copaxone (n=2), Tysabri (n=1), Gilenya (n=1), Intravenous Immunoglobulin (IVIG) (n=1), and Rituximab (n=1). Of note, the same patient receiving IVIG was also receiving Rituximab. Please see **Table 1** for clinical and demographic characteristics of participants.

Intervention Program

All participants were offered the option of accessing the internet-based Cogmed RM program on their personal computer or using a laptop provided by the research investigators. The Cogmed RM version is typically used with children aged 7-17 years, but can also be used with young adults. Training sessions were scheduled over a 5-6 week period to allow for holidays, illness, and slow progress. All training occurred in participants' homes and effort was made by the investigators to schedule the training to occur at a time that was convenient for participants.

Description and intensity of intervention program. The Cogmed RM program consists of twelve visually-engaging WM exercises of which the user completes eight per day; exercises rotate each day to provide novelty and maintain interest. WM exercises (described below) tap into both visuo-spatial WM (remembering the position of objects) and auditory-verbal WM (remembering letters and digits). Task difficulty is matched to the individual's current memory span on a trial-by-trial basis for each task. Difficulty level for each task gets adjusted automatically and continuously as the participant improves during each session (i.e., the span of each trial will increase from 6 to 7, for example, as mastery is achieved). Likewise, the difficulty level will adjust downward if it is too difficult and the participant is failing several trials (i.e., the span may drop down from 5 to 4, for example).

Participants were asked to complete 25 sessions of Cogmed training, with each session lasting approximately 45 minutes. It was recommended that participants try to complete the four to five sessions every week, for a total of 25 sessions over five weeks, or up to seven weeks if necessary. Participants could choose whichever 4-5 days of the 7-day week on which they completed training, and their training schedule could vary from week to week. For example, one week a participant could choose to complete training on five consecutive days and subsequently take two days off from training. The following week, the same participant could choose to complete training on three consecutive days, take the next day off from training, resume training thereafter for two days, and finally take the seventh day off from training. Participants were asked to not complete more than one training session per day. Participants could also alter the time of day at which they train, to accommodate their schedule and convenience. At the time that the study was completed, training extending beyond 6 weeks was considered to be less effective because the intensity of the training was thought to be diluted. More recent preliminary evidence, however, suggests that weekly intensity can be reduced to three times a week over a lengthier period of time without affecting training outcomes (personal communication with Stina Soderqvist, Pearson consultant, 2015; based on unpublished report). Participants complete 15 trials per exercise (thus 15 trials x 8 exercises = 120 trials each day that the training is undertaken). For the purpose of the current study, the number of trials completed, rather than training time, was controlled. Short breaks lasting up to a few minutes at a time to ensure sustained and intense training may be taken in between exercises and not in the middle of an exercise underway. The program logs a participant out after 10 minutes of inactivity. Break times were monitored by Training Coaches, who have undergone training and certification to administer the Cogmed program to participants and who support participants throughout their training process under the supervision of a registered psychologist. Any concerns identified by Training Coaches (i.e., unusually short or long break times) were discussed with participants. All of the above training procedures are recommended by the Cogmed program developers as based on an analysis of prior Cogmed training data collected over a seven year period for the purpose of demonstrating optimal training dose for achieving maximum effects (Pearson, 2012).

The user chooses the order in which the eight exercises are completed each day. The Cogmed program automatically provides auditory instructions on the first training day, when a participant selects an exercise. On subsequent training days, participants can select the instructions button on the screen to hear them again if need be. Instructions may be read aloud as many times as needed. The Cogmed program provides immediate and continuous visual performance-based feedback to participants through a ‘level meter’ that stays on the right-hand side of the computer screen throughout an exercise. Each level represents the number of items that a participant needs to remember (e.g., at level 3, the participant will need to remember the order in which three lamps light up). The level on the meter goes up and down, as a participant remembers sequences correctly or incorrectly, respectively. There is also an 'exercise progress bar' that stays on the bottom left-hand corner of the computer screen throughout an exercise which shows how much of that exercise a participant has completed, and how much they have left to complete. The Cogmed program also presents an individual's best score relative to previous scores once they complete an exercise. Immediate, auditory feedback is also provided throughout exercises (e.g., "Way to go!" or "You were close!"). An optional Robo Racing game that does not tax working memory is also included as a reward at the completion of each training session. In this game, the main robot races against other robots on tracks and fuel for racing is awarded based on a participant's performance on training exercises. Thus, the better the participant performs on the training exercises, the more energy they accumulate for the racing game, which in turn, allows them more opportunities to race.

Of the 12 Cogmed RM exercises, eight of them are visual-spatial and the other four auditory-verbal. The following is a description of the 12 Cogmed exercises (provided courtesy of www.cogmed.com) organized by visual-spatial versus auditory-verbal type**:**

Visual-spatial Cogmed exercises.

1. ***Visual Data Link.*** A number of lamps are highlighted in succession. The participant needs to remember the order in which they came on. When the program says, "Your turn'', the participant clicks on the lamps in the same order.

2.***Sorter.*** Certain boxes are highlighted and numbers are revealed. They then disappear. When the program says, “Your turn”, the participant starts by clicking on the box that contains the number 1, then the box that contains the number 2, 3, and so on, in numerical order.

3.***Asteroids.*** A number of moving asteroids light up in succession. The participant needs to remember the order in which the shapes lit up. When the program says, “Your turn”, the participant clicks on the shapes in the same order they lit up.

4.***Rotating Dots.*** The participant sees some circles rotating. The circles light up in a specific order. They also move, so the participant needs to keep track of their initial position. The participant then clicks on the circles in the same order they lit up, although they are now in new positions.

5.***Rotating Data Link.*** A number of lamps are highlighted in succession. The participant needs to remember the order in which they came on. Before the participant provides an answer, the entire panel rotates 90 degrees. When the program says, “Your turn”, the participant clicks on the circles in the same order in which they came on, but has to remember that the panel has rotated 90 degrees. The participant has to click on the circles in the correct order, although they are now in new positions.

6.***3D Cube.*** A number of panels light up in different colours in succession. At the same time, the cube is turning toward each panel that lights up. The participant needs to remember the order in which the panels lit up. When the program says, “Your turn”, the participant clicks on the panels in the same order.

7.***Data Room.*** Some of the lamps in a 3-dimensional room light up. The participant needs to remember the order and then click on the lamps in the order that they lit up.

8.***Space Whack.*** Monsters randomly appear in craters, but before they appear, they let out a little cloud of gas. The participant needs to remember the order of the gas clouds to be able to prepare to hit the monsters over the head when they do appear.

Auditory-verbal Cogmed exercises.

9.***Stabilizer.*** Certain letters are read aloud. When a letter is read, it is displayed in the middle of a circle, and at the same time, a corresponding light is lit. After all the letters have been read, one of them will be displayed once again in the middle. The participant needs to remember which light came on when he/she heard that particular letter. The participant responds by clicking on the correct light.

10.***Decoder.*** Certain letters are read aloud, and at the same time, the letter lights up. The participant needs to remember the letters he/she hears and then select the letters by clicking on them. For example, if the letters heard were, "D, P, E", the first letter was 'D' so the participant would have to select that letter from the three options next to the first light. At the next light, he/she would select 'P', the second letter. Finally, he/she would select 'E' from the options next to the third light. Of note, Decoder is only offered during sessions 1-5 of computer training.

11.***Input Module.*** A number of digits are read out loud in succession. The participant needs to listen carefully and try to remember the order in which they were read. When the program says, "Your turn", the participant should click on the numbered buttons in reverse order. For example, if the digits, "3,7", were read out loud, the participant should click on '7' and then '3'.

12.***Input Module with Lid.*** This is a different version of Input Module. The numbers are read out loud, however, the participant cannot see the numbered buttons as they are read (i.e., a lid comes down and covers them). The numbers will appear when it is the participant's turn to click on the numbered buttons in reverse order.

Support during training phase. A certified **Training Coach** (Bravina or an RA) was assigned to each participant prior to commencing training. Certification by Pearson was required in order to be able to administer the Cogmed program to participants. To become certified, Training Coaches had to do the following: read material provided by Pearson that pertained to the current literature regarding Cogmed; complete training with the Cogmed program to gain a better sense of what participants would experience (5 days minimum were required out of the 25 training days); and attend a four-hour interactive webinar (hosted by Pearson) in order to learn about the role of the Training Coach at the various phases of a participant's training process. More current certification also requires passing a Cogmed coaching procedure test. The Cogmed Training Web is an online platform accessed by Training Coaches to view each participant's training data and to monitor their progress. After obtaining consent for study participation, the Training Coach logged into the Cogmed Training Web and created a training profile for the participant. Gender, as well as birth month and date, were entered, to create a training profile. The participant's name was never entered into the Cogmed Training Web, in order to protect their privacy. Once a profile was created, a Training ID and password was provided by the program so that the Training Coach could keep track of and access that particular individual's training data. Training Coaches had access to a participant's Training Calendar, Training Statistics – Summary, and Exercise Statistics – Summary. The Training Calendar showed on which days training sessions occurred. The Training Statistics – Summary showed how much time was spent on ‘active’ training versus breaks for each training session. The Exercise Statistics – Summary provided information about the time of day each session was carried out, the order in which exercises were completed each session, trial-by-trial performance for each exercise (i.e., successful, failed, or missed trial) and the level reached on each exercise during each training session.

Prior to commencing training, an in-person start-up session was scheduled for each participant with their Training Coach (scheduled for the same time as their baseline assessment) in order to familiarize them with the Cogmed program. During this start-up session: (i) participants were provided with their program login information and Training Coach contact information; (ii) working memory and its importance were discussed; (iii) participants were shown how to access and navigate through Cogmed on their laptop, as well as given the opportunity to try out all 12 exercises; (iv) the expectations for training were discussed; and (v) a tentative schedule for training sessions and weekly phone calls with their Training Coach was developed. At the end of this session, participants were provided with a reference handout to take home describing how to use the program, a calendar outlining the scheduled phone calls, and headphones and/or an external mouse, if they did not have this equipment at home.

The Training Coach made weekly phone contact with individuals to check-in about the last five training days. Each call lasted approximately 10-20 minutes. Prior to each weekly scheduled phone call with a participant, the Training Coach logged into the Cogmed Training Web to examine the participant’s data thoroughly. A checklist was used to collect information on the following: whether the participant trained all the days he/she was supposed to; approximately how long the training was taking and what time of day training was being carried out; how long a participant was spending on breaks; profile of the participant’s performance (i.e., number of successful, failed, and missed trials); what the Improvement Index was at; whether there were signs of technical and/or other difficulties; and what recommendations/feedback should be provided to the participant during the upcoming phone call. Please see **Appendix A** for this checklist.

During the weekly call, the Training Coach asked questions about how the last five training days went overall, which exercises the participant liked and disliked, whether there were any specific problems and/or disruptions/interruptions, and whether the participant had any questions or concerns. During the weekly call, the Training Coach also administered a brief questionnaire to inquire about the onset of new symptoms related to disease ('yes' or 'no'; if 'yes', explain), onset of any changes in day-to-day life (e.g., break-up with a partner, death in family, etc.) ['yes' or 'no'; if 'yes', explain], and to monitor participants' engagement with the program. The latter information was collected using a 5-point Likert scale, where '1' indicated 'none', '2' indicated 'little', '3' indicated 'moderate', '4' indicated 'almost all/almost fully', and '5' indicated 'all/fully'. Participants were asked to rate their overall '*amount of effort*' used during the last five training days, using the Likert scale. This process was repeated for their overall levels of '*attention during training',* '*enjoyment with the program'*, and '*motivation to do training',* with respect to the last five training days. Of note, this questionnaire was used more as a monitoring tool and not an outcome measure. For example, if a participant endorsed very low levels of effort, attention, enjoyment, and/or motivation to do training, the Training Coach would follow up with the participant and provide recommendations around training. Please see **Appendix B** for Patient Weekly Follow-Up Questionnaire. The Training Coach also inquired about cognitive, physical, and overall level of fatigue, using the PedsQL Multidimensional Fatigue Scale (Varni et al., 1999), in order to monitor a participant's general level of fatigue.

The PedsQL Multidimensional Fatigue Scale is described in detail below. Finally, the date and time of the next scheduled phone call was confirmed. The total number of phone calls with the Training Coach was recorded for each participant.

Baseline and follow-up cognitive assessments occurred at York University in a quiet test room. To maintain continuity and manageability of the many facets of this study, entry of participants was staggered by pretesting, treating, and post-testing subgroups of participants. Psychological testing (50 min) and completion of questionnaires (25 min) occurred on the same day.

Clinical-Demographic Information

Socio-demographic information was assessed using a general questionnaire that was completed by the patient if he/she was over the age of 16 or by a parent/guardian if he/she was under the age of 16 (see **Appendix C**). Participants also completed questionnaires about mood using the Center for Epidemiologic Studies Depression Scale for Children (CES-DC) (Weissman, Orvaschel, & Padian, 1980) and 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 et al., 1999). The CES-DC, developed specifically for children and adolescents (Weissman et al., 1980), is a 20-item scale used to screen for depression. In response to 20 statements, youth are asked to indicate how strongly they have felt a certain way during the past week (e.g., “I was bothered by things that don’t usually bother me.”). A 4-point Likert scale is utilized (0 = not at all; 1 = a little; 2 = some; 3 = a lot). Four items are phrased positively (e.g., “I felt happy”), and thus are reverse scored (0 = a lot; 1 = some; 2 = a little; 3 = not at all). Points for each of the 20 items are summed to provide an overall score. Elevated scores indicate increasing levels of depressive symptomatology, with scores over 15 being indicative of significant levels of depressive symptoms (Weissman et al., 1980). This scale has been validated with individuals aged 6 – 23 years old (Shahid, Wilkinson, Marcu, & Shapiro, 2012).

The PedsQL Multidimensional Fatigue Scale is a generic symptom-specific instrument that was designed to measure fatigue in patients, from the perspective of children, adolescents, and their parents (Varni, Burwinke, & Szer, 2004). The 18-item scale consists of three subscales (six items per subscale): 1) General Fatigue (e.g., ‘‘I feel too tired to do things that I like to do.’’); 2) Sleep/Rest Fatigue (e.g., ‘‘I feel tired when I wake up in the morning.’’); and 3) Cognitive Fatigue (e.g., ‘‘It is hard for me to remember what people tell me.’’) (Varni & Limbers, 2008). A 5-point Likert scale is utilized (0 = never a problem; 1 = almost never a problem;

2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem). Points for each of the 18 items are summed to provide an overall total fatigue score, with elevated scores being indicative of increased fatigue symptomatology. Scores between 36-53 are indicative of moderate fatigue symptomatology whereas scores over 54 are indicative of severe fatigue symptomatology (personal communication, Dr. Ann Yeh, SickKids). Self-report versions exist for ages 5 – 7, 8 – 12, 13 – 18, and 18 – 25. Given the age range of the sample in the present study, either the 13 – 18 or 18 – 25 version was administered, according to the age of the individual. There were no differences between the two versions. Of note, this questionnaire was administered repeatedly to monitor participants’ general level of fatigue during the course of the intervention period.

Raw scores were used for the CES-D and for each fatigue dimension and for total fatigue score on the PedsQL.

In order to help determine whether participants in the study were representative of the general population, an estimate of socioeconomic status was determined based on parental education and occupational status using the validated Barratt Simplified Measure of Social Status (BSMSS) (Barratt, 2006). The BSMSS is a measure of social status, which is a proxy for socio-economic status. The BSMSS is built on previous work of Hollingshead (Hollingshead, 1957; Hollingshead, 1975), who created a simple measure of social status that was based on marital status, retired/employed status, educational attainment, and occupational prestige. Two important changes have been made to the Hollingshead Four Factor measure of social status to transform it into the BSMSS: 1) The list of occupations has been updated (still 9 divisions); and 2) In recognition of the generational shift in social status, the BSMSS accounts for an individual's parent's educational attainment and occupational prestige, combining that with an individual's own educational attainment and occupational prestige. Scores are assigned based on parents', spouse's, and an individual's educational attainment and occupations (with higher scores being associated with higher levels of educational and professional attainment). These scores are then combined to produce a total score that ranges between 8 and 66, with elevated scores indicating increased socio-economic status.

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. The EDSS is a scale that is used to evaluate the extent of disability in individuals with MS, by quantifying disability in eight functional systems (i.e., pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, and other). Assigned scores can range from 0.0 to 10.0, with increasing score indicating increasing disability (i.e., 0.0 indicates a normal neurological exam; 10.0 indicates death due to MS). EDSS scores ranging from 1.0 – 4.5 describe individuals who are fully ambulatory; and scores ranging from 5.0 – 9.5 are defined by the particular impairment to ambulation (e.g., score of 5.5 indicates 'ambulatory for 100 metres').

Brain volume data were also available for all participants in the current study since they had all participated in a neuroimaging study that was conducted within six months of the current study. Participants underwent magnetic resonance imaging (MRI) using a 3.0 Tesla Siemens Tim Trio scanner at York University. 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 1x1x3 mm^3 voxel size, along with a matching 2D turbo FLAIR sequence with TR=9000 ms, TE=88 ms, TI=2407.5 ms. For the purpose of the current study, normalized brain volume (reported as a z-score) and total brain lesion volumes for each participant were included as clinical variables to characterize the sample. Methods regarding the quantification of these MRI metrics and normalization techniques can be found in another paper (Aubert-Broche et al., 2011).

Assessments

Pre-training baseline assessment. The baseline assessment was performed within one week before the initiation of Cogmed training. At the baseline visit, each participant completed a set of standardized clinical tests and questionnaires. *Tests were selected on the basis of the following criteria*: (i) sound psychometric properties, including high reliability (i.e., consistency across test administrations) and validity (i.e., shown to relate to the psychological construct under study); (ii) repeatable, with minimal effect of practice; (iii) brief enough to permit comprehensive sampling across various cognitive domains; and (iv) reduced reliance on complex linguistic processing. Many of the measures included in the proposed test battery have been used in prior work with pediatric-onset MS patients, and thus, we can ensure the feasibility, reliability, and validity of the measures for use with the current population (Till et al., 2011b; Till et al., 2012).

Specific cognitive tests that were chosen for inclusion in this study were separated into two primary domains of interest: i) WM (both verbal and visuo-spatial); and ii) Non-WM. Raw scores were used to examine change between the pre- and post-training assessment for each individual. As well, overall measures of Global Cognitive Functioning, fatigue, depression, and motivation were included. A description of each measure is provided below:

Global cognitive functioning. The two-subtest version of the Wechsler Abbreviated Scale of Intelligence (WASI; (Wechsler, 1999) was used to estimate IQ. This measure was used at the baseline assessment to ascertain that participants had the necessary cognitive functioning to complete the intervention program (i.e., IQ level >70). The two-subtest version of the WASI consists of Vocabulary and Matrix Reasoning subtests. On Vocabulary, participants are asked to describe what words of increasing difficulty mean. On Matrix Reasoning, participants are asked to choose from an array of choices the one pattern that best completes the incomplete matrix. The total score on Vocabulary is the total number of points awarded for responses. The total score on Matrix Reasoning is the number of items correct. Of note, the FSIQ-2 estimate is strongly correlated with the FSIQ-4 estimate (Kamphaus, 2005).

The Motivation for Change Questionnaire (MCQ) (Gard et al., 2005) was used to measure the strength of a participant's motivation for change in their life situation [pre-training assessment only]. The MCQ was originally developed as a 48-item screening instrument, in order to identify the strength of one's motivation for change in his/her life situation (28 items) and work situation (20 items). It was developed for use in clinical practice to help set realistic treatment goals and to choose optimal treatment strategies (Grahn & Gard, 2008). For the purposes of the current study, only part one of the MCQ (i.e., items pertaining to one's life situation) was administered. This section of 28 items consists of seven subscales, to which individuals respond either 'yes' or 'no' (or 'true' or 'false' on some items): social support (e.g., "Do you get social support from your relatives in your daily life?"), mastery in life (e.g., "Do you feel competent to handle your life situation?"), challenges in life (e.g., "Is curiosity important for you when you want to do something?"), control in life (e.g., "Do you control your life situation?"), values in life ("Do your values and beliefs help you when you want to change?"), self-efficacy (e.g., "What happens in the future depends to a great extent on myself"), and self-confidence (e.g., "I feel that I have many good personal qualities"). 'Yes' or 'true' responses are awarded a point (with the exception of two items which are reverse scored) and summed to generate a total score out of 28. Elevated scores indicate an increased motivation for change in one's life situation.

Working memory measures.

1) Wide Range Assessment of Memory and Learning – Second Edition (WRAML-2): Finger Windows. The WRAML-2 (Sheslow & Adams, 2003) is designed to assess verbal and visual attention and memory skills in both children and adults. The Finger Windows subtest from the WRAML-2 was used in the current study as a measure of visual-spatial WM. On this subtest, participants are asked to duplicate increasingly long series of visual patterns which an examiner demonstrates by putting his/her finger through asymmetrically located holes on a card. The total score is the number of correct sequences. The standardization sample consisted of 1200 individuals, collected between 2002 and 2003. Test-retest reliability for Finger Windows is 0.69.

2) Woodcock-Johnson III Tests of Cognitive Abilities (WJ-III COG): Auditory Working Memory. Measures from the WJ III COG (Woodcock, McGrew, & Mather, 2001) are designed to assess cognitive processes in children and adults. One of its subtests, Auditory Working Memory, is a test of WM as well as divided attention in the auditory modality. Participants hear a series of digits and words (e.g., “cat, 2, dog, mouse, 7, 1”) and they must reorder the series into a two-part sequence, starting with words and then providing digits in the same order as which they were heard (i.e., “cat, dog, mouse, 2, 7, 1”). Each item is scored out of 2 points, with one point awarded for repeating all of the words correctly and another point awarded for repeating all of the digits. The total score is the number of points awarded. Reliability coefficient (i.e. an index of the precision with which relative standing or position in a group is estimated) is high for this measure, falling between 0.86 to 0.88 for individuals between the ages of 14-29 (McGrew, Schrank, & Woodcock, 2007).

3) Woodcock-Johnson III Tests of Cognitive Abilities: Numbers Reversed. Numbers Reversed is a WM test as well as test of attentional capacity in the auditory modality. Participants hear a series of digits and they must present the series in the reverse order in which it was heard. The total score is the number of sequences correct. Reliability coefficient is high for this measure, falling between 0.80 to 0.90 for individuals between the ages of 14-29 (McGrew et al., 2007).

The temporal stability of the WJ III COG subtests over a one-day interval is for the most part adequate to strong (ranging from 0.72-0.85 for ages 14-17), though test-retest reliabilities were only calculated for six speeded measures from the WJ III COG and are not provided for the two subtests used in the current study (McGrew et al., 2007).

Non-working memory measures.

1) Woodcock-Johnson III Tests of Cognitive Abilities: Decision Speed. This is a test of processing speed which follows a cancellation task paradigm and uses small line drawings of common objects. Participants must locate two items that are similar conceptually, among distractors, row by row, under time constraints (e.g., shoe and boot). The total score is the number of items correct within a maximum of 180 seconds. For ages 14-17, and for ages 26-79, test-retest reliability for this subtest is considered adequate ($r = .80$ and $r = .72$, respectively) (McGrew et al., 2007). These test-retest reliabilities are based on a one-day testing interval of 55 and 48 subjects per age groups. This short interval was chosen to minimize variability due to state or trait changes, according to the authors. Reliability coefficient is also high for this measure, falling between 0.80 to 0.90 for individuals between the ages of 14-29 (McGrew et al., 2007).

2) Benton Judgment of Line Orientation. The Benton Judgment of Line Orientation (Benton, Sivan, Hamsher, Varney, & Spreen, 1983) is a standardized measure of visuo-spatial judgment. Two forms of the test, Form H and Form V, consist of the same 30 items presented in a different order. On each form, items are presented in a generally ascending order of difficulty. Participants are asked to identify which two partial lines are in the same direction and point in the same direction as two target lines. The total score is the number of items correct. Corrected split-half reliability of Form H in a sample of 40 individuals was 0.94; the same statistic for Form V in a sample of 124 individuals was 0.89. Thirty-seven individuals were given both forms of the test, with the interval between test and retesting ranging from 6 hours to 21 days. The test-retest reliability coefficient was 0.90. On this test, average adult performance is reached by the age of 13 years.

3*) Doors and People Test: Names.* The Doors and People Test (DPT; (Baddeley, Emslie, & Nimmo-Smith, 1994) is designed to assess visual and verbal recall and recognition, and can be used with individuals aged 16-80+ years. One of its subtests, Names, is a measure of verbal recognition. Here, participants are presented with two series of written names and immediately after each series, are asked to identify target names from an array of distractors. The second series is more challenging than the first because the target names and distractors are more similar. The total score is the number of target names correctly recognized. There is no information provided in the manual about test-retest reliability. The authors of the test were contacted in order to obtain this information, however, they indicated that they did not collect it due to financial and methodological limitations. A study of performance on the Names subtest across 20 successive test sessions conducted in healthy subjects and patients with severe head injury (Wilson, Watson, Baddeley, Emslie, & Evans, 2000) found that patients showed a decline in performance on Names compared to healthy subjects, probably due to an interference effect.

Post-training assessment. Soon after completing Cogmed training and no later than two weeks post-training, clinical measures and all questionnaires that were administered in the pre-training assessment were repeated (with the exception of IQ, Motivation for Change, case history measures, and brain imaging). When possible, the same examiner who administered the measures at baseline also administered the measures at the post-training assessment, in order to decrease the potential for examiner-related variance in test administration. Participants were usually assessed at the same time of day as their baseline assessment (assessments often took place on Saturday or Sunday mornings), in order to decrease the potential for variance in test performance. For both time-points, the same version of the test was administered; alternate versions of all tests were not available, with the exception of the Benton Judgment of Line Orientation test which had an alternate version. At the post-training assessment, participants were interviewed by Bravina about their experiences with the intervention, and were invited to provide feedback about areas of the intervention which may be improved. A list of questions was developed by drawing from feasibility surveys used in previous Cogmed studies (Hardy et al., 2013; Kronenberger et al., 2011) and interview questions used in previous studies examining participant experiences following implementation of a novel psychotherapy program (Carr et al., 2012; Finucane & Mercer, 2006). The list of questions was administered to each participant using a semi-structured approach, thus allowing for flexibility in questioning throughout interviews. These semi-structured interviews lasted between 15 to 30 minutes and consisted of the following 13 open-ended questions:

1) What did you think about the training procedure?

2) What did you find helpful about the training procedure?

3) What did you find unhelpful about the training procedure?

4) What barriers did you face during the training procedure?

5) What supports and/or reinforcements did you have to continue your training sessions and how were they completed?

6) Where was training usually completed?

7) Were there usually any distractions inside/outside the room where testing was completed?

8) What activity were you usually doing before beginning training? What activity were you usually doing after completing training?

9) How did the training impact your daily routine?

10) How did the training impact your social life?

11) How do you think you benefited from the program?

12) Are there any aspects of the rehabilitation program that you would change?

13) Do you have any other comments or suggestions?

In keeping with the principles of semi-structured interviewing, participants were allowed as much time as required to respond to each of the questions. With consent from participants, participants' responses were recorded on an audio recording device. The audio recordings were transcribed verbatim, entered into Microsoft Word, and analysed qualitatively using QSR Nvivo 10 qualitative analysis software.

Exercise-Specific Training Outcomes

Cogmed calculates a training index that is based on a participant's performance on one particular visual-spatial WM exercise and one of two particular auditory-verbal WM exercises (the exercise with the better performance is selected out of the two) practiced during the training period. The reason why these exercises are selected by the Cogmed program is not entirely clear. Given that the training index is based on performance on only 2-3 of the 12 Cogmed exercises, an alternate method of capturing performance across all of the Cogmed exercises was used (with the exception of one exercise (*Decoder*), which is not included in the training after session 5 of the training program). Consistent with the methodology of a previous pilot study on working memory training for children (Kronenberger et al., 2011), a performance improvement value was obtained for each of the 12 Cogmed exercises by subtracting the mean training level on the third day for an exercise from the *mean training level* for a participant's best performance in the final five days of that exercise. The third day was used as a baseline score in order to allow for a participant's performance to stabilize. Mean training levels for each day were provided in the Exercise Statistics – Summary section of Cogmed Training Web. The *mean training level* is based on the average number of items that a participant needs to remember (e.g., number span or visual span) during a training day for that exercise. Since the Cogmed program uses an adaptive training algorithm, the number of units presented to a participant (i.e., span length) directly corresponds to the number of units that a participant can remember correctly. Thus, exercise-specific performance improvement values were indicative of improvement in memory units remembered for a particular exercise between the beginning and end of the training period. The mean of the performance improvement values for the eight visual-spatial WM Cogmed exercises was calculated in order to obtain an overall measure of visuo-spatial WM ('Visuo-Spatial WM Performance Improvement'). The mean of the performance improvement values for three verbal WM Cogmed exercises was calculated in order to obtain an overall measure of verbal WM ('Verbal WM Performance Improvement').

Training data were downloaded from the Cogmed server for each participant and exported into SPSS for data analysis. The data included trial-by-trial information about performance for each day of training across exercises (i.e., trial level, successful trials, failed trials, missed trials) as well as overall training summary statistics (i.e., total number of calendar days to complete training, mean active time per day, and mean pause time per day**). Table 2** presents a list and description of all Cogmed-specific outcomes in the study.

Reimbursement and Feedback

Following each assessment, participants received a cash gift of $20 (for a total of $40 if both assessments were completed). One month following the completion of the intervention, participants received a brief summary report describing their performance on standardized clinical tests (from the baseline assessment).

Data Analysis

Quantitative data were analyzed using SPSS Version 21.0. Descriptive statistics (frequencies, means, medians and standard deviations) were first calculated for the demographic, clinical, neurocognitive, and other health-related variables in order to characterize the overall patient sample.

Objective 1: Assessment of feasibility, adherence, and training tolerance. Objective 1 was addressed by examining descriptive statistics for several training outcomes: number of sessions completed per individual, length of training period (in calendar days), number of phone calls with Training Coach, training time per session, break time per session, and treatment adherence and tolerance. Adherence to treatment was defined as completion of at least 80% (20 sessions) of the required sessions within 40 calendar days or less, whereas training tolerance was assessed by examining the ratio of time spent on active training compared to time spent on breaks, during sessions. Since the recommended guidelines by Cogmed are that the ratio of time spent on active training to time spent on breaks should be greater than or equal to 2:1, in this study, an individual who exhibited a ratio greater than or equal to 2:1 was described as "tolerating the training well" (i.e., suggesting that they did not need a disproportionate amount of break time to get through training).

Objective 2: Description of qualitative experiences of participants undergoing the program. In order to address Objective 2, data from exit interviews were analysed qualitatively using QSR Nvivo 10 software. The analysis of qualitative experiences was based on the constant comparative method (Glaser, 1965), which aims to find patterns and commonalities between participants' experiences. With this method, there is an emphasis on developing a theory that is grounded in data (Boeije, 2002), and concepts are the basic units of analysis rather than the actual data per se, because it is through the conceptualization of data that theory is developed (Corbin & Strauss, 1990). That is, incidents, events, and occurrences are analyzed as potential indicators of phenomena (which are then assigned conceptual labels). This method of comparing and contrasting involves forming categories, establishing the boundaries of categories, assigning segments to categories, summarizing the content of each category, and finding negative evidence (Tesch, 1990). The goal of this method is to identify and discern conceptual categories, and to discover patterns (Tesch, 1990).

The analysis of qualitative experiences in the current study was modeled after the approach utilized by previous researchers (Pienaar, Swanepoel, van Rensburg, & Heunis, 2012) that involved: i) an inductive analysis of the obtained information whereby codes were clustered according to commonalities in order to establish critical themes and subcategories; ii) comparative, cross-analysis of identified subcategories and themes between respondents in order to establish consistency, iii) the use of counting procedures called 'descriptive counting' in order to increase meaning and value of the information obtained; and iv) interpretation of the data Interview transcripts were imported into QSR Nvivo 10 and through the use of the 'Autocode' function, separate 'nodes" (virtual data storage containers) were created for all responses from participants to each interview question. This enabled data from interview transcripts to be organized by question so as to look across all respondents and their answers in order to identify consistencies and differences.

Each node was analyzed for emerging themes. The process of analysis involved three types of coding: open, axial and selective coding to develop a set of themes (Plexico, Manning, & Levitt, 2009; Strauss & Corbin, 1990). Aptly described by Pandit (1996), *open coding* refers to the earliest phase of labelling and categorizing of phenomena as indicated by the data. Here, data are initially broken down by asking simple questions such as what, where, how much, when, etc., and then similar incidents are grouped together and assigned the same conceptual label. While open coding dissects data into concepts and categories, it is succeeded by *axial coding* which involves putting those data back together in novel ways to develop main categories and sub-categories. Finally, *selective coding* involves integrating the categories that have been developed in order to form the initial theoretical framework. Pandit (1996) points out that these three types of coding are analytic, hence, a researcher may not necessarily move from open through axial to selective coding in a strict, consecutive manner.

As a preliminary, broadbrush method of analysis in order to help with the identification of themes, a word frequency query was run for all respondents' responses to a particular interview question. Before running each word frequency query, the settings were modified in order to group together words with similar meanings (e.g., help, assist), and to exclude less significant words (e.g., a, in) from query results. The results of the word frequency query returned the most frequent words used in response to a question across all responses, and helped orient the researcher to emerging themes. For example, for the interview question: "What are your overall thoughts about the training procedure?", the most frequently used word in response was "long". This entire process was repeated for each interview question.

As a second, more in-depth method of analysis, responses to each interview question were read and segmented into units of text containing one main meaning. Each of the meaning units was then assigned a subtheme to identify discrete ideas and phenomena. Nodes were created to organize data reflecting similar subthemes. Emergent themes and subthemes were examined. Due to the subjective nature of qualitative research and the potential for researcher bias, the analysis employed in the present study remained primarily descriptive rather than interpretive, in order to allow participants' narratives to speak for themselves (Finucane &

Mercer, 2006). The frequency with which themes and subthemes were referenced across participants was recorded for each interview question and was plotted in individual bar graphs.

Safeguards were put in place in an attempt to minimize the impact of researcher bias on interpretation of the results. Such methods included: discussion of biases and expected findings with the supervising psychologist (C. Till) who did not attend the interviews nor participate in coaching, the use of a standard list of questions that was administered to every participant, audio recording of participant responses, transcription of interviews verbatim (and by another person) prior to any type of analysis, and having a different person (RA) serve as coach from the interviewer when possible.

Objective 3: Contribution of individual characteristics and qualitative experiences to overall outcome. In order to examine how individual factors (clinical and neurocognitive characteristics, mood, fatigue, and motivation for change), together with qualitative experiences, may contribute to overall outcome with the training program, a large table of outcomes was generated to search for patterns among the data. The data were summarized in one table in order to see if any of the demographic, clinical, neuropsychological, or subjective outcomes were associated with overall training outcomes with Cogmed. This aim was simply to generate hypotheses and to provide some commentary on the relationship between variables. Moreover, it was hoped that the table would bridge the qualitative experience with the other data collected. Participants were organized by improvement on Cogmed (most improved to least improved) and then specific factors were examined to look for any trends in the data. Correlations among individual factors were also examined to aid in the process of generating hypotheses about relationships between variables.

Objective 4: Assessment of Cogmed performance outcomes. Objective 4 was addressed by examining descriptive statistics for performance improvement values on visuo-spatial and verbal WM computer exercises. Performance improvement values were obtained for each of the 11 Cogmed exercises by subtracting the mean training level on the third day for an exercise from the *mean training level* for a participant's best performance in the final five days of that exercise. An overall measure of visuo-spatial WM ('Visuo-Spatial WM Performance Improvement') was calculated by taking the mean of the performance improvement values for the eight visual-spatial WM Cogmed exercises. Similarly, an overall measure of verbal WM ('Verbal WM Performance Improvement)' was calculated by taking the mean of the performance improvement values for the three verbal WM Cogmed exercises.

Objective 5: Preliminary efficacy. In order to investigate preliminary efficacy of Cogmed, individual differences on neuropsychological measures from the pre-training to post-training assessment were calculated using the Reliable Change Index (RCI) method (Jacobson & Truax, 1991). The RCI was calculated using the following formula:

$$\text{RCI} = (x2 - x1)/Sdiff,$$

where *x1* represents a participant's baseline score, *x2* represents the participant's post-training score, and *Sdiff* is the *SE* of that difference. 'Reliable change' occurs if the absolute value of the difference score between baseline and post-training exceeds the *SD* of the test-retest difference of the sample, multiplied by the z-score cutoff (i.e., $z = 1.645$) (Temkin, Heaton, Grant, & Dikmen, 1999). The *Sdiff* value can be computed from the *SE* of measurement, which is a function of the initial *SD* of the measure and its reliability, according to the following formula:

$Sdiff = \sqrt{2(Se)^2}$,where $Se = s\sqrt{(1 - r_{xx})}$.

The difference score is considered to be statistically significant if the score exceeds the RCI value in either the positive (‘improved’) or negative (‘decline’) direction. Difference scores falling outside of this prediction interval are considered to indicate change that is due to chance.

Chapter Four: Results

Patient Flow Through Study

Seventeen of 45 eligible patients (38%) met inclusion criteria. Of these, nine (53%) agreed to participate, five (29%) declined participation, and three (18%) did not respond. Reasons for declining participation included competing academic demands (n=3), not interested in participating in any further research studies (n=1), and no perceived benefits of participating (n=1). Patients who did not participate were similar in age and represented a similar female-to-male distribution (i.e., two-to-one ratio) as those who did participate. Patient flow and figures are shown in a consort diagram (**Figure 3**).

Demographic Information

The study sample included six females and three males with pediatric-onset MS. The decision to include the nine participants was, in part, based on either objective and/or subjective evidence of cognitive difficulty on any one measure included in the screening battery (please see **Appendix D** for performance outcomes for each participant). As shown in Table 3, the mean age at the time of baseline assessment was 18.8 years (SD = 3.9, range = 14.2-24.7). The mean socioeconomic status score was 38.8 (SD = 38.8) with the lowest score being 10.5 and the highest being 61.0. The mean IQ was within the average range (M = 101.6, SD = 14.4, range = 78-122). The mean score on the Motivation for Change Questionnaire was 24.8 (SD = 2.9), with the lowest score being 19 and the highest being 27.

Mood at baseline assessment, as assessed by the CES-D scale, fell within the mild depression range (M = 16.1, SD = 11.5). Mild symptoms of depression (as classified by a score between 16-26 points on the CES-D) were reported by two patients, whereas more elevated symptoms of depression (classified by a score above 27 points) were reported by one patient. Regarding symptoms of fatigue, the average score on the Total Fatigue scale was 34.4 (SD = 10.9), indicating mild levels of fatigue. However, considerable variability was noted in scores, with mild symptoms of fatigue (as classified by a score below 36 points) being reported by five patients and moderate symptoms of fatigue (as classified by a score between 36-53 points) being reported by 4 patients. None of the patients reported severe symptoms of fatigue (as classified by a score greater than 54). In general, fatigue symptoms did not differ between any of the individual fatigue scales of the Varni PedsQL (General Fatigue, Cognitive Fatigue and Sleep/Rest Fatigue scales), however, the most variability was seen on the Cognitive Fatigue scale (M = 11.3 points, SD = 5.1, range = 3-21).

Structural MRI Measures

Regarding MRI variables, the mean normalized brain volume (z-score) was -0.62 (SD = 0.69), indicating an average brain volume relative to age and sex-matched controls. However, closer examination of the data revealed a large range (i.e., z-scores between -1.74 to 0.39), with 3 of the 9 patients having considerably smaller brain volumes (i.e., z-score greater than one standard deviation from age- and sex-matched healthy controls). T1 and T2 lesion volumes were log-transformed because the distributions were non-normal. The median of the log-transformed T1 lesion volume data was 3.30mm^3 (SD = 1.19). Closer examination of the data revealed a large range (i.e., values between 0.0 to 4.0 mm^3). The median of the log-transformed T2 lesion volume data was 3.58 mm^3 (SD = 0.79). Closer examination of the data revealed a large range (i.e., values between 1.7 to 4.4 mm^3).

Objective 1: Adherence, Training Tolerance, and Feasibility

Table 3 presents overall training outcomes of participants (N=9).

Adherence. Of the 9 participants enrolled in the study, 6 (67%) were adherent to training, as defined by completion of at least 80% (20 sessions) of the required sessions within 40 calendar days or less, and 3 (33%) were considered non-adherent. Of the six patients who were considered adherent, all completed all training sessions (25 sessions) within an average of 41 calendar days (range: 34-50). Two non-adherent participants were female: one of these participants completed five sessions of training over five calendar days, and did not return to complete the post-training neuropsychological assessment because she lived in another city, however, she completed the exit interview over the phone; the other participant completed 24 sessions of training over 140 calendar days (Note: 80% of training was completed within 136 calendar days), and she did return to complete the post-training neuropsychological assessment as well as exit interview. The third non-adherent participant was male: he completed 20 sessions over 135 calendar days, and he did return to complete the post-training neuropsychological assessment as well as exit interview.

Independent-Samples Mann-Whitney U-tests for equality of means for training outcomes revealed that adherent individuals completed a significantly higher number of training sessions (M = 25.0, SD = 0) and phone calls with their Coach (M = 5.0, SD = 1.1) than non-adherent individuals (M = 16.3, SD = 10.0 and M = 2.3, SD = 1.1, respectively; both p values <.05). No differences in other training outcomes (e.g., length of training period, active time, pause time, Visuo-spatial WM Performance Improvement, Verbal WM Performance Improvement), nor demographic or clinical characteristics were found between adherent and non-adherent individuals. Therefore, the analyses of Cogmed outcomes below (Objective 4) include complete data from eight participants (Note: The individual who completed five days of training was excluded as there was insufficient training data to draw meaningful conclusions, and this individual did not complete the post-training neuropsychological assessment). Though length of training period was not found to differ significantly between adherent and non-adherent individuals, it should be noted that there was marked variability among the non-adherent group due to the non-adherent individual who only completed five calendar days of training (i.e., non-adherent group mean = 93.33 days, SD = 76.54 days). Results of Independent-Samples Mann-Whitney U-tests for equality of means for all training outcomes can be found in **Appendix E.**

Tolerance. The mean active time per day was 45.4 minutes (SD = 5.7, 38.3-54.4), suggesting that patients can complete Cogmed within recommended time limits. Moreover, the median pause time per day was 6.8 minutes (SD = 10.1) and ranged from 2.0-34.9, with only one participant taking a pause that was, on average, beyond nine minutes per day. Thus, patients appeared able to complete the Cogmed training in less than 60 minutes (approximately 45 minutes of active training plus 7 minutes of breaks). Of the 9 participants enrolled in the study, 8 (89%) appeared to tolerat the training well, defined by the ratio of time spent on active training to time spent on breaks being greater than or equal to 2:1, and 1 (11%) was considered as not tolerating the training well (i.e., the individual who took beyond 9 minutes of breaks). Of note, 6 of the 9 individuals who appeared to tolerat the training well were also considered adherent to the training, while 2 of the 9 who appeared to tolerate the training well were considered non-adherent. This finding highlights the importance of considering both adherence and tolerance when assessing feasibility of treatment. The participant considered to not tolerate the treatment well was male and also considered non-adherent: his mean active training time was 54 minutes while his mean break time was 35 minutes, resulting in a ratio equal to 1.5. The disproportionate time spent on breaks by this individual suggests that he might have struggled to complete the training program.

Overall, implementation of the Cogmed program was deemed feasible in a subset of patients with pediatric-onset MS. The findings from the present study suggest that the training program may be well tolerated by most of the patients (i.e., 8 out of 9 in this study), however, there appear to be challenges with adherence in some patients (i.e. one-third of the sample were non-adherent). Individuals deemed both adherent to training and able to tolerate the treatment well were able to complete the training program within the recommended time-frame (i.e., 5-6 weeks) and recommended time limits (i.e., under 60 minutes, including breaks).

Objective 2: Subjective Experiences

A large quantity of data were accumulated from the interview transcripts. After merging nodes with interview questions which appeared to tap into the same concept, a total of 12 nodes were generated, as per the subheaders below. The 12 nodes were analyzed and seven main themes and various subthemes emerged which are summarised in **Figures 4 (a)-(h).** It is important to note that although the themes and subthemes are discussed separately, the themes described were not experienced in isolation. Instead, many were experienced in conjunction with others.

Theme 1: Overall thoughts about training program. The overall thoughts provided by participants were classified as either positive or negative aspects of the training program, and will be discussed below.

1.1 Positive aspects. Almost all of the participants acknowledged that the training program was helpful overall in one or more ways (n = 8).

> *"It helped a lot with my memory" (COG_06).*
>
> *"I really liked it because it was what I was looking for – something that would work my memory which it did… and it kind of helped me realize my own limits" (COG_09).*
>
> *"It helped in tests too, I can remember a lot better" (COG_12).*

One non-adherent participant, who completed five days of training, did not find the program helpful in the immediate term.

> *"It didn't really [help] …maybe it'll help me in the long run but it didn't really help me with anything while doing it or afterwards." (COG_07).*

Almost half of the participants (n = 4) referenced the subtheme of enjoyment of either the overall training program or particular training exercises.

"…most of the time I did enjoy doing it…I did enjoy eighty percent of the games, there were a couple that I didn't, you know, I had bad days with but I mostly enjoyed it." (COG_02).

"The one exercise when you were doing the – when the little space men were popping out from the meteorite, that was actually one of my favourites. It was fun to tap them on their head…" (COG_10).

Two participants, who were considered adherent and tolerant of the training, acknowledged how the training intervention addressed their concerns about their own cognitive decline.

"Keep up the good work. I'm glad that more research is being done into this [cognitive rehabilitation], especially when it comes to different cognitive effects…'cause with MS for me, that's my biggest worry…cognitive issues… what's gonna happen up here [pointing to head] 10 years down the road. The biggest thing with MS is it's caused me to shift in what I did, I mean I used to be in really theoretical mathematics and physics, but I just can't…the logic…I can't do it…it's caused me to shift into other sciences. So that's my biggest concern, any way I can improve my cognitive ability for me is very important." (COG_09).

"I think that a lot of people should do this – I don't know what the results are gonna say, I didn't think that this [training] would help me as much as it did…the other thing too is that I guess I just didn't realize, I thought the cognitive problems that I had were somewhat rigid, in that – I was like 'ah well, these are the problems that I have, I have

MS,' – and I guess I just didn't realize there was a way to strategize. The main thing I wanna say is everybody with MS should do this" (COG_05).

One participant, who was considered both adherent and tolerant of the training, described the training as being rewarding.

"I enjoyed doing some of the exercises. It was kind of rewarding, I started off only remembering three numbers and…sometimes – some exercises I was just remembering [more] numbers so it was pretty rewarding to see yourself do that much better from the start." (COG_08).

1.2 Negative aspects. More than half of all participants (n = 5) acknowledged that the individual training sessions themselves were time-consuming.

"I felt that one session itself was long, so after four or five games I'd be kind of tired" (COG_02).

"I think the fact that I had to do so many activities and the activities themselves took so long, I was just…like when is this gonna be over? They wanted you to do it for so long, and it took so long, that it just became a nuisance rather than something I would do no problem." (COG_07).

The training was also described by participants as being repetitive (n = 3), challenging (n = 2), tiring (n = 2), and feeling like a chore (n = 2).

"I think it was so repetitive I couldn't stay focused through it because I didn't wanna do it." (COG_07).

"While I was doing it [training], it definitely felt repetitive…like I'm not gonna lie I wasn't really looking forward to doing it, it was kind of like 'ah I have to do my study now'." (COG_09).

"It definitely took a lot of dedication, I can't say it was easy 'cause it was challenging. It was pretty tiring, but I felt, every day after I did training, honestly I felt similar to how I feel after I go to the gym. Like I felt tired, I felt like I'd worked out, but I felt good." (COG_05).

"I thought that it was a bit long, so, I felt like I just became very tired by the end." (COG_02).

"Overall, I mean, I liked it. To be completely honest it was a little intense near the end [of the training period], it became more of a chore than I guess something you just wanted to do; kind of near the end there it got a little difficult to do." (COG_09).

One participant who was considered non-adherent and not tolerant of the training (he completed twenty days of training over 135 days), described the training as being boring.

"It was kind of boring, I wish it was funner 'cause it takes a lot of time to do it… some of the programs, when you have to do some of the word stuff and number stuff inside of his chest, it was kind of boring to do it because it took a long time to do and finish." (COG_10).

Theme 2: Participant-reported change. A range of changes was reported by participants across various domains of functioning. Only one non-adherent participant, who completed five days of training, felt that nothing had changed.

"I didn't do it for long, I only did it for a week. I guess I didn't really benefit from it – not that it wasn't a good program, I just didn't do it for long." (COG_07).

2.1 Working memory. Almost all of the participants (n = 8) referenced the subtheme of working memory. They acknowledged improvements in their working memory, particularly with respect to retention (i.e., holding information "online") and retrieval (sometimes after manipulation and/or interference), over short periods of time.

> *"As soon as I got to day twenty, even in the middle of training, I noticed even when I was at work how much improved my memory was…for example, if I needed to measure something at work, sometimes I would – before the training – I would forget as soon as I went to go make the cut, 'cause I was framing and I would go to cut a piece of wood and totally forget, but ever since I started that [training], I could remember it [measurement] all the time." (COG_08).*
>
> *"I think my memory has benefited. I can remember things… I think the thing that I noticed most is when somebody tells me something I can remember it. Before, I would sometimes forget and now I can – especially with phone numbers – I can just remember them so easily." (COG_08).*
>
> *"Remembering sequences of numbers: I definitely noticed that…it [training] definitely has helped me in remembering I guess dates let's say." (COG_09).*
>
> *"I found it the most helpful for school really. I'm not really good at taking notes and I noticed that usually when professors are giving lectures and it's sort of rapid fire, I'll start a note and then have to go to another point and usually when I go back to the previous point to try to finish – fill in the blanks – I can't. I noticed just the other day in class that I was able to go back to the previous point and finish the point, and I had remembered what he [the professor] had said two three minutes ago…which never happened before so I think that that was definitely one of the greatest things." (COG_05).*
>
> *"Sometimes my mom asks me to go upstairs and get her something, and before that [training], I would go upstairs and totally forget what she told me and I would go back*

and ask her what she told me to get. And when I was doing it [training], I pretty much kind of remembered she wanted me to get her the phone or I don't know water or something like that." (COG_10).

"I've noticed that I'm a quicker reader and not just that I read quicker, it's that I'm able to retain more." (COG_05).

"They [school] would give me an agenda and I would probably lose it. So I would try and just remember something they told me and sometimes I would just totally forget when they [projects] were due…so when I was doing the exercise [training], when the teacher was talking to me and telling me about projects and stuff like that, I can remember and just say I have to bring a Bristol board to school tomorrow." (COG_10).

"Yeah it helped a lot with my memory…especially like the Space Whack and all that stuff, it's in order so you have to try and take a photograph in your memory and then picture it so it helped a lot with my memory." (COG_06).

2.2 Learning. More than half of all participants (n = 5) referenced the subtheme of learning. They acknowledged changes in how they were learning new information, and how these changes were beneficial to them in school-related work.

"I found that it was during exam time that I did it [training], and I felt that the way I was trying to memorize things or absorb what just happened – like the visual things – it kind of helped me prep for exams, sort of in a way that I kind of developed a different way of studying. My studying habits sort of changed. I felt that I wasn't using the conventional ways of studying anymore for certain things…so with the visual things, I would make a path and then I would just let it kind of sink in…I would just kind of look at the

information rather than repeat it constantly. I felt that I was doing a different way of studying…it felt different from the usual way." (COG_02).

"Actually I think it's a psychology class I'm working on…just remembering different aspects of course material… it [training] definitely helped me with that, and when I'm reading I found I have a little bit more retention – I don't have to re-read the same passage as much." (COG_09).

"I can remember numbers better, stuff like that…access I guess. I can remember definitions for tests really well…really quickly, actually…if I need to know something word-for-word, I can remember it word-for-word, really quickly" (COG_12).

2.3 Strategies. Two adherent participants, who were considered tolerant of the training, referenced the subtheme of strategies. They acknowledged how training pushed them to develop strategies to remember information which they can subsequently use in other activities.

"I found different strategies to get me through the memory tasks. Before, I didn't really have the initiative to work on my memory. I was trying to get better with my memory so I came up with new rules to help me remember things…like the list of numbers and having you repeat it back…as the numbers went by I kept repeating the same numbers over and over again in my head just so I would have a list of the set of numbers in my head. That way I could relay it back backwards." (COG_15).

"I think another way it's [training] benefitted me is it's given me some new techniques for remembering – remembering content, remembering numbers…a lot of these little tricks that I used I developed during training." (COG_09).

2.4 Speed of processing. Two adherent participants who were considered tolerant of the training referenced the subtheme of speed of processing. They acknowledged increases in their speed of processing, with respect to different tasks.

> *"Well I'm noticing I'm quicker too. People used to always say I'm witty and then now, more and more, I'm noticing even just in conversations – 'cause like a lot of my friends are really smart and I always felt really dumb – and now I feel smarter. (COG_05).*

> *"I also find that I'm reading quicker too, than I used to…'cause reading would make me tired before …I love reading…but I was always a slow reader, and I've noticed that I'm a quicker reader." (COG_05).*

> *"If I need to know something word-for-word, I can remember it word-for-word, really quickly" (COG_12).*

2.5 Attention. One adherent participant who was considered tolerant of the training referenced the subtheme of attention. She acknowledged improvements in her overall focus.

> *"It [training] forced me to focus for an hour, to focus on these intense brain training tasks…I feel more alert to tell you the truth…I feel like I'm awake now." (COG_05).*

2.6 Psychological changes. Three participants who were considered adherent and tolerant of the training made reference to changes in their psychological functioning. They acknowledged increases in their ability to cope with stress (n = 2), gains in their self-confidence (n = 2), increases in their energy level (n = 1), and better insight into their cognitive functioning (n = 1).

> *"I would get really frustrated that I wouldn't get things and it would just affect me…but I felt that it [training] helped with my tolerance when I didn't get something…my frustration tolerance – it became better." (COG_02).*

"It [training] kind of sort of helped with just relaxing because I did do it just before I went to bed, and it just kind of got my mind off school so I kinda went to bed with a clear mind…fell asleep much faster. It made me feel less stressed." (COG_02).

"First semester [prior to training], I was somewhat overwhelmed…I'm finding this semester it's still a lot but I am, I'm less exhausted at the end of my day; I can do classes and I can go home and the thought of homework doesn't make me cringe…like I can actually tackle some homework. I have a lot of anxiety too so it [training] kind of helped my anxiety." (COG_05).

"I felt that whenever I did well on the training, I felt better about myself so it was kind of like a self-esteem boost." (COG_02).

"I think even just for myself I think I proved a lot of things to myself. I wasn't sure if I'd be able to do it [training] and continue to excel into five weeks and also when you said five times a week I was like that sounds like a lot… and I think I surprised myself that I was able to do it in the five weeks…this is a real confidence booster for me." (COG_05).

"This [training] gave me more energy…I feel like I have the mental energy" (COG_05).

"I realized that maybe I need to work on my memory a lot more, whereas before I was just like 'eh my memory is fine, everyone's just telling me that'. It also benefitted me by 'cause when I was more tired some days, my training scores weren't great whereas when I was more alert it was better. So I think I realized I need more sleep to strengthen my mind and memory…" (COG_15).

Theme 3: Barriers to training. Almost all of the participants (n = 8) reported experiencing barriers to training, some external and others internal. One participant who was considered adherent and tolerant of the training reported not experiencing any barriers.

3.1 External barriers. More than half of all participants (n = 5) acknowledged that work- or school-related activities (e.g., homework, exams) and/or extracurricular activities served as barriers to doing training.

> *"Work was one [barrier] alongside school. Balancing all of that – it just became tough to squeeze it [training] in some days, but then again I didn't have to train every single day so I just had to manage my time well. But then with school, homework, with all that added stress – it just became a bit hard" (COG_02).*
>
> *"I think it [barriers] was mostly physical 'cause some days I didn't have time to do it [training], 'cause mostly of all the soccer and sports and stuff I had to do…and I'd have homework a lot of the days too. So some days that I missed [training], it's mostly 'cause I had either soccer or homework" (COG_06).*
>
> *"Pretty much soccer and school came in the way…because sometimes my mom would tell me do it [training] but then I had to study for a test and do a lot of homework, and do some projects and stuff like that. So I had to put it [training] off and then I would go and try to do it but I'd have to go to sleep for school." (COG_10).*

One non-adherent participant who was not considered to tolerate the training well acknowledged that technical difficulties prevented him from completing training.

> *"My computer broke and I forgot the password so I couldn't really finish the rest of them [training sessions]. And then when I was trying to do it on my home computer, I forgot*

the password and I couldn't find it in the binder where I put all my stuff like that" (COG_10).

3.2 Internal barriers. Almost half of all participants (n = 4) acknowledged that low motivation sometimes served as a barrier to doing training.

"If I was in class for seven hours, I didn't want to do it [training]." (COG_05).

"Sometimes I wasn't the most motivated to do it [training] ...sometimes if I didn't really wanna do it, I don't think I did as well as other days where I'd be like alright I think I'll do pretty well today. The days where I didn't really feel motivated to do it, I didn't do as well, I don't think." (COG_08).

"Maybe I'd go out for a weekend or somewhere…but also the other half of the time I either just forgot about it or I just didn't want to do it so I kept pushing it off until ten 'o clock at night" (COG_09).

Two non-adherent participants acknowledged that they found the exercises boring, which served as a barrier to training.

"I guess after a while it [training] gets a bit boring. Some days are worse than others but it just gets boring. Sometimes I don't – most times I wouldn't mind – but sometimes I just would want to get it over with so I just wouldn't try." (COG_12).

"I found it [training] boring, so when I wanted to go train I wouldn't want to do it so I would pretty much just stop doing it and put it off for another day…and then do that and keep putting it for another day." (COG_10).

One participant who was considered adherent and tolerant of the training acknowledged that fatigue served as a barrier to do training.

"One of the biggest barriers was just, I think, my mental fatigue…I would get tired really – I would be halfway through a trial and I would be just so tired, and some days I would leave training until the end of the day just 'cause I had so many things to do that day…I definitely noticed when I would do training that – if I was tired – because it's so difficult, I would just be like 'I do not want to do this today'." (COG_05).

Theme 4: Supports/reinforcements for training. All of the participants (n = 9) acknowledged utilizing supports and/or reinforcements, some of which were extrinsic, while others were intrinsic.

4.1 Extrinsic supports/reinforcements. More than half of all participants (n = 5) acknowledged using social reinforcements for doing training. These reinforcements included motivation from their Cogmed Coach (n = 4) and praise and/or motivation from a friend/relative (n = 4).

"When I talked to A.S. [coach], she was really enthusiastic… I guess she was trying to motivate me to keep going...she was super polite and nice" (COG_07).

"I got support from B.K. [coach]...B.K was encouraging" (COG_08).

"I had some support from my mom…she would tell me 'good job'; she's saying 'you're doing a good thing to help other people too with this'… also, she's saying she's really proud of me [of] how I'm doing this." (COG_06).

"She [mom] was pretty much the person that made me get all the way to 20 [sessions] because she kept saying I have to do it, it'll help my memory and stuff like that. She kept on saying it was important so that was pretty much the motivation do it." (COG_10).

One third of all participants (n = 3) acknowledged using food rewards for training.

"I was pretty much eating cookies while I was doing it [training]. Every time I did one [exercise], I would eat a cookie and keep doing it" (COG_10).

"I reward something [training] with some sugar after" (COG_06).

One third of all participants (n = 3) acknowledged using some form of technology as a reward or motivator for training (e.g., watching TV, playing computer games, listening to music).

"I have a lot of TV shows that I keep up with and so if I knew that there was a new episode of something on that day, I would say 'okay, I am gonna watch this episode but only if I do training first'." (COG_05).

"As soon as I was done [training], I would go on the internet and maybe go to different websites that I usually go to reward myself, or go watch TV or listen to music on the computer as soon as I was done." (COG_08).

Two participants acknowledged using the program's built-in auditory feedback as motivators to do training.

"I actually enjoyed that man [voice providing feedback], even though it was a bit 'campy'…I understood that it was for kids but also it was nice to hear 'very good!'…or if I would mess up a trial but be really close, he would say 'ah you were so close!' And it [was] actually like, 'oh thanks man!' (COG_05).

"It [built-in feedback] was actually really lame at first, but then the more I kept doing it, it was more encouraging…when he was like 'three in a row!', I was like okay maybe I can do four in a row and…it just did motivate me. So at first I did find it a little cheesy but then it was really comforting." (COG_02).

One non-adherent participant acknowledged using monetary rewards for part of her training.

"My mom would give me five dollars every time I finished it [training session]…she stopped after awhile" (COG_12).

4.2 Intrinsic supports/reinforcements. One third of all participants (n = 3) acknowledged using intrinsic motivation in conjunction with external supports to complete training.

"I didn't feel the need like I had to get support from friends and external people…I felt like I could do it [training] myself and it could just be, just be more satisfying." (COG_02).

"I really motivated myself more, knowing that I help other people". (COG_06).

"I don't have anybody pushing me anymore so I either have to do it or it's just not gonna be done." (COG_09).

One participant also acknowledged aiming to surpass his scores on the training exercises as a motivator.

"Breaking my high scores was definitely helpful…that would motivate me to do more and try harder and break my high score… so that was a huge motivator to do well." (COG_09).

Theme 5: Distractions during training. Most of the participants (n = 7) reported experiencing distractions during training, however, none of the distractions were significant enough to invalidate training. Two participants – one adherent and one non-adherent – reported no distractions. Of the participants who reported experiencing distractions, two acknowledged experiencing internal distractions.

5.1 External distractions. Almost half of all participants (n = 4) reported that their families (including pets) sometimes distracted them while they were doing training at home.

"Luckily I wasn't interrupted too often, but I was interrupted a lot in between exercises luckily or I would finish a sequence and before I started another one I would get interrupted. My family's not very good at just leaving me alone. They would just come in my room." (COG_09).

"At home, sometimes my cat would jump up on the laptop screen and she would obstruct my view, and I got her out of the way but it – I think it overall – over the five weeks, it probably only affected four different trials tops." (COG_05).

Almost half of all participants (n = 4) reported that general noise outside the room in which they were doing training sometimes distracted them.

"A couple times I had to do the trials at school just because I was on campus all day and I had engagements at night. And so I found that even though I was wearing headphones and I was in a quiet area, outside noise disrupted me a few times…just people chatting, whatever, they're on their way to wherever they're going." (COG_05).

"The first couple days 'cause I didn't use headphones, like it just came out of the computer speakers, so I could hear cars passing by which was kind of distracting. I have a big pair of headphones so I just used those, and from then on right to the end, I didn't have any distractions at all." (COG_08).

Two participants acknowledged being distracted by an electronic device (i.e. cell phone or TV) during training.

"When I was downstairs, they [family] would be watching TV…I couldn't really hear 'cause I have noise cancelling headphones but I would casually look up to it and then start watching like that…[for] a minute and then it would get probably boring because

they watch Tree House and stuff like that. So I would glance up to it and then go back to the work that I was doing." (COG_10).

Of note, almost half of all participants (n = 4) reported that they turned their cell phone off or put it on silent during training.

"Sometimes, if I had my phone beside, I'd turn my phone off so my phone doesn't vibrate so I don't get any phone calls. Or I'd leave it downstairs with my mom. So I could do it [training] quicker or I don't have any distractions." (COG_06).

"I usually put it [cell phone] on my desk and I was on my bed doing the program so I just kind of left it alone for an hour or so." (COG_07).

5.2 Internal distractions. Two participants who were considered adherent and tolerant of the training acknowledged being distracted by occasional internal or "wandering" thoughts while they were doing training.

"Sometimes, when I was busy at school or as of late with the essay and stuff, I would find my mind drifting a bit…I would be in the middle of an exercise and I'd be like 'that's a good point for my essay; no you have to focus!' And so I think I distracted myself a little bit… so I guess sort of internal distractions…but that's also where breaks came in handy." (COG_05).

"I guess sometimes I would distract myself. I'd be doing the study and I'd distract myself – something as simple as, 'what am I gonna have for dinner?' And then just, the whole series is just gone. I find that a bit of an issue…sometimes I have a lot of wandering thoughts when I'm focusing on something; something will wander through and I'll have to fight [to] push it away and stay focused." (COG_09).

Theme 6: Burden of training. All of the participants (n = 9) acknowledged that the training did not impede their social lives.

> *"I can't think of an impact…I'd still go out and see people, it [training] didn't really interfere with anything." (COG_09).*
>
> *"I would just do the training and then go outside, or go play soccer with my team, or go on the computer on Facebook and stuff like that. It [training] didn't really affect my social life." (COG_10).*

Two thirds of all the participants (n = 6) acknowledged that the training did not impede their daily routine.

> *"It [training] didn't really [impact]…I was just kind of setting aside time to do it but it didn't really impact my daily routine at all." (COG_07).*
>
> *"It [training] didn't really impact it [routine] that much…I said it before, it kind of got off to being a little long, sometimes an hour, an hour and a half…but again, it didn't really impact my daily routine. Maybe more recently it took me away from studying but again, if I wasn't doing the study I would just be doing something else, probably something not productive" (COG_09).*

Two participants who were considered adherent and tolerant of the training acknowledged that training made their days busier than usual.

> *"It made things busy…'cause sometimes I'd come home from school [and] I have a project to finish, and then I'll do it [training], and then I have soccer, and then I have to finish homework. So I had a busy schedule doing it, but it wasn't bad…it was okay." (COG_06).*

Of note, one participant acknowledged that planning her schedule in order to incorporate training helped her become more productive in other activities.

> *"There's a happy ending to this story because it [training] actually changed my routine [in] that it'd be more productive for me…whereas I would read things the night before I go to class, I'll end up taking let's say two three hours before my class and do the reading then…because of when I chose to do my cognitive training, it actually put me in a better position for classes" (COG_05).*

Theme 7: Factors participants would change. All of the participants (n = 9) acknowledged suggestions for change with respect to the duration of training and/or program-specific features.

7.1 Duration. One third of all participants (n = 3) acknowledged that the individual training sessions themselves were lengthy and they would prefer shorter sessions and/or less exercises.

> *"I think just making the activities shorter by themselves…I'm not sure how much information you guys need…that would probably explain why the activities themselves were so long but I think that if they were shorter and it took less time, it would be a lot easier to stick with it for five weeks." (COG_07).*
>
> *"Instead of the eight exercises that you do a day, it would be better if it was six…'cause sometimes eight felt like a lot." (COG_08).*

Of note, one adherent participant who was considered tolerant of the training felt that the duration of the training program was adequate and necessary in order to have any effect.

> *"I wouldn't change the length 'cause I believe it would have to at least be that long to really have any effect, I find" (COG_09).*

6.2 Program features. One third of all participants (n = 3) acknowledged that some training exercises were either too similar or had to be done every day and could be changed or eliminated from the program to prevent repetitiveness (i.e. Input Module and Input Module With Lid).

> *"I think there were the two things [exercises] that were really similar, like the ones with the lid and then without the lid. I thought those were really similar, so maybe keep the one with the lid in or the one without the lid in…[or] take one of those and maybe put a new one in, a new activity." (COG_06).*
>
> *"I don't know how much control you guys have over what trials [or] exercises appear again and again, but when I had input module with lid and input module, those ones I felt were – the entire time I had them…and I understand they're part of the training but for me it just got really annoying" (COG_05).*

One adherent participant who was considered as tolerant of the training acknowledged that the training exercises which involved rotating stimuli often made her nauseous, and to consider eliminating these, particularly when using the program with patients with similar symptoms.

> *"…the ones [exercises] that rotate – I guess you'll have to wait and see what other patients say – I feel like for people with symptoms…dizziness and vertigo and stuff…it can set it off a bit, it was just unpleasant." (COG_05)."*

One non-adherent participant who was not considered as tolerating the training well, and who completed 20 days of training over 135 days, acknowledged that the look and design of the program should be updated to be more appealing to youth.

> *"I wish most of them [exercises] were funner or appealed to kids of my generation 'cause most of them are all retro…I wish it was more modern, I would've finished it faster. Try and tie it in to stuff that are happening nowadays, maybe do one exercise that's based on*

> *some video games like Call of Duty or stuff like that. Or try and tie it in with electronic people like Pac-Man games and stuff like that. I wish it wasn't like, everything based on the robot in the middle. I wish it was all individual games and you could move away from the robot…" (COG_10).*

One participant who was considered adherent and tolerant of the training expressed a wish for the exercises to be more random in nature in order to maximize gains.

> *"I don't know how it's [program] designed but when I was working through a lot of the exercises, like for example, I think it's the five-by-five squares and they light up in a specific order, you get to trace it. When they light up, let's say for example I'm doing five lights, you have four that light up right next to each other, so maybe the fifth one is just a repeat. So I find that when the lights are close together it's easier for me to remember 'cause I just remember 'okay so line and then you go back one'. And then the next one might be all over the place but sometimes I'll get it when they're right next to each other maybe three times in a row…it gets me up to seven lights 'cause if they're all really close, I find I have an easier time remembering them. And then they'll all spread out again and I'll do really poorly and I'll maybe go back down to five lights. I would like it to be a little more random, the exercises themselves to be a little more random just to prevent people like me from developing those little tricks, 'cause it would force you to remember it more." (COG_09).*

One adherent participant who was considered tolerant of the training reported enjoying the Robo Racing reward game and expressed a wish for more of the game.

"More Robo Racing, that's something I want, definitely more Robo Racing!" (COG_05).

Objective 3: Individual Characteristics and Experiences

Table 4 presents demographic, clinical, neuropsychological, training, and experience-related outcomes for all nine participants (N.B. COG_07 was left in the table for the sake of completeness, however, this participant's data was not analyzed below due to a great proportion of missing data). The table is organized by Cogmed verbal WM improvement values for each participant, from those showing least improvement to those showing greatest improvement. Each column represents a different participant. Verbal WM improvement was chosen because, as a group, patients showed greater increases in verbal WM capacity from baseline compared to visual-spatial WM, and thus, there was a greater range of values to work from. It is important to keep in mind that the table served as a means of looking at the data collectively to try to establish trends that might suggest associations between the variables worthy of further study. This was obviously done to generate hypotheses, and so, is very exploratory in nature.

From the table, a consistent pattern appears to emerge between improvement on Cogmed and normalized brain volume, such that the participant showing the least improvement also has the lowest normalized brain volume (i.e., COG_15), while the participant showing the greatest improvement has the highest normalized brain volume in the group (i.e., COG_09). This finding draws attention to the importance of considering how much someone with more compromise to brain white and grey matter (and thus, perhaps lower neural reserve) can profit from computerized cognitive rehabilitation efforts that focus on restoring damaged neural networks.

From the table, it is also very interesting to note that the participant who showed the least improvement on Cogmed (i.e., COG_15) also had the youngest age at disease onset in the group (7.6 years old), longest disease duration (10.3 years), highest number of relapses (i.e., 13), and lowest normalized brain volume (z = -1.74). These findings highlight some important clinical characteristics to consider when deciding whether an individual can benefit from cognitive rehabilitation, and suggest that an individual with a more compromised brain and who has had the disease for longer, may benefit less (i.e., shower lesser gains) from rehabilitation efforts that focus solely on promoting neuroplastic restorative processes. Perhaps, such an individual may profit more from rehabilitation efforts focused on the utilization of compensatory strategies.

From the table, it is also interesting to note that the participant who showed the greatest improvement had the oldest age at disease onset (18.5 years), and highest normalized brain volume (z = 0.19), and IQ within the High Average range. These findings lend support to the hypothesis that participants who have less brain atrophy (as well as higher cognitive reserve), might be the ones who can benefit the most from cognitive rehabilitation efforts aimed at restoring damaged networks rather than compensating for them. Another interesting finding from the table is that the individual who was deemed as both non-adherent and non-tolerant of the training (i.e., COG_10), had normalized brain volume in the Low Average range (z = -1.15) and IQ falling in the Borderline range (IQ = 78). These findings suggest that there may be positive associations among brain reserve, cognitive reserve, and training outcomes.

It is also interesting to note that this participant, and another participant who was deemed as non-adherent, both described the training as ‘boring’. This finding suggests that some individuals who appear to be more extrinsically motivated may struggle to adhere to a challenging training program unless they find it engaging and/or stimulating. On a related note, it is interesting to note that the three individuals who showed the greatest improvement on Cogmed, and who were all deemed as adherent and as tolerating the training well, all acknowledged the use of intrinsic motivation during training (e.g., self-satisfaction, self-improvement, sense of helping others). This finding suggests that there may be a positive association between intrinsic motivation, and adherence and tolerance, with those being more intrinsically motivated as being able to adhere to and tolerate a challenging and intense training program. One final note is that the MCQ did not appear to predict performance on Cogmed, nor adherence or tolerance, suggesting that perhaps this is not an adequate tool for assessing one's motivation for cognitive training in this particular patient sample.

Taken together, these findings suggest that clinical characteristics (i.e., brain and cognitive reserve), disease characteristics (i.e., age at disease onset, disease duration, relapses) and motivation (ie., intrinsic vs. extrinsic) may be important variables in predicting performance outcomes (i.e., improvement, adherence, and tolerance) on Cogmed and warrant further study. For detailed case summaries of each participant, please refer to **Appendix G.**

Objective 4: Assessment of Cogmed Performance Outcomes

The following Cogmed exercise-specific outcomes are based on the eight participants who completed at least 20 sessions (regardless of time to complete the training program). The decision to include the two non-adherent patients in the analysis was based on the fact that their performance outcomes on the Cogmed exercises were no different from those who completed all the training sessions within 40 days or less. As previously described in the Methods section, exercise-specific performance improvement values were indicative of improvement in the number of memory units remembered for a particular exercise between the beginning and end of the training period. The mean of the performance improvement values for the eight visual-spatial WM Cogmed exercises was calculated in order to obtain an overall measure of visuo-spatial WM (‘Visuo-Spatial WM Performance Improvement’). The mean of the performance improvement values for three verbal WM Cogmed exercises was calculated in order to obtain an overall measure of verbal WM (‘Verbal WM Performance Improvement’).

All eight participants showed improved WM task performance from baseline on at least 7 of 11 exercises. As shown in Table 5, the greatest increases were observed on the verbal WM exercises, in comparison to the visuo-spatial WM exercises, across participants. The mean value of the Verbal WM Performance Improvement was 2.38 units (SD = 1.53) and ranged from 0.43-5.69. The mean value of the Visuo-Spatial WM Performance Improvement was 1.05 units (SD = 0.45) and ranged from 0.18-1.58.

As expected, changes on the specific Cogmed exercises were generally consistent in terms of showing improved Cogmed performance across each exercise. With respect to the verbal exercises, all eight participants showed improved WM task performance from baseline on *Input Module* (mean performance improvement value = 2.91 units, SD = 1.92, range: 0.67-7.01) and *Input Module with Lid* (mean performance improvement value = 2.50 units, SD = 1.25, range: 1.13-4.84) whereas all but one patient showed an increase on *Stabilizer* (mean performance improvement value = 1.74 units, SD = 1.90, range = -0.52-5.23). Mean improvement values are shown in **Table 5** for each Cogmed exercise and for each participant.

With respect to the visual-spatial exercises, participants showed improved WM task performance from baseline across all exercises over the course of the training period. As shown in Table 5, all participants exhibited improved WM task performance from baseline on *Sorter* (mean performance improvement value = 1.23 units, SD = 0.70, range: 0.28-2.47), *Rotating Dots* (mean performance improvement value = 1.38 units, SD = 0.54, range: 0.18-1.88), *Rotating Data Link* (mean performance improvement value = 1.37 units, SD = 0.70, range: 0.33-2.53), *Data Room* (mean performance improvement value = 0.97 units, SD = 0.54, range: 0.12-1.88), and *Visual Data Link*, (mean performance improvement value = 1.47 units, SD = 0.82, range = -0.39-2.21).

Change in performance was slightly more variable (with one or two patients showing no change or a negative change over time) on three exercises that are introduced later on in the training period. It is possible that reduced exposure to these exercises, compared with the other exercises, could account for the observed smaller improvement values on these exercises. Mean performance improvement values were 0.74 units (SD = 0.54, range = -0.11-1.28) for *Space Whack*, 0.62 units (SD = 0.89, range = -0.47-1.96) for *3D Cube*, and 0.60 units (SD = 0.78, range = -0.55-1.66) for *Asteroids.*

Objective 5: Preliminary Efficacy

Individual differences: Reliable Change Index (RCI). Table 6 presents the number (proportion) of individuals showing significant cognitive change using the Reliable Change Index (RCI) method. In terms of individual performance on non-trained WM measures, clinically significant improvement was observed in 1/8 individuals on Finger Windows (i.e., COG_15), 2/8 individuals on Auditory Working Memory (i.e., COG_05 and COG_09), and 1/7 individuals (i.e., COG_09) on Numbers Reversed. Clinically significant decline was not observed in any of the individuals on the non-trained or trained measures of WM. In terms of individual performance on the non-WM measures, clinically significant improvement was not observed in any of the individuals on any of the measures. Of note, clinically significant decline was observed in 1/8 individuals on Benton Judgment of Line Orientation (i.e., COG_15).

By themselves, the results of this particular approach to analysis provide very limited evidence for the efficacy of Cogmed in this study sample. It is important to consider the high degree of self-reported change in WM that was found, when speaking to efficacy. This issue will be discussed further below.

Chapter Five: Discussion

The current study sought to introduce a working memory (WM) training program (Cogmed) that is novel to the MS population in order to investigate feasibility, subjective experiences, and individual characteristics related to training outcomes, as well examine preliminary efficacy of Cogmed in individuals with pediatric-onset MS. Participants in the current study demonstrated general adherence to and tolerance of the intensive intervention, and were able to complete training within 5-6 weeks. All but one participant reported improvements in their WM, and all individuals described no interference of the cognitive training on their social lives. Clinical characteristics (i.e., normalized brain volume), disease characteristics (i.e., age at disease onset, disease duration, number of relapses), and intrinsic motivation emerged as potentially important variables in predicting adherence, tolerance, and improvement on Cogmed. Feasibility, training experiences, individual characteristics that may predict training outcomes, and efficacy of Cogmed will be now be given further consideration.

Feasibility

The present study suggests that implementation of the Cogmed program is feasible for individuals with pediatric-onset MS, as demonstrated by their general adherence to and tolerance of this intensive, home-based intervention. Overall, adherence level was 67%, and all individuals, with the exception of one, were considered to tolerate the training well. Moreover, time to completion of the overall program by adherent and tolerant individuals in this study met the recommended Cogmed guidelines of 5-6 weeks. The same was true for the length of individual sessions completed by adherent and tolerant individuals in this study (i.e., training sessions on average lasted just under an hour, including breaks). These results suggest that home-based, computerized cognitive training can be successfully implemented in roughly two-thirds of young people with MS who are identified as having cognitive impairment. It is noteworthy that two individuals who were considered non-adherent described training as being boring, and a third individual who was considered non-adherent felt that the training program was not helpful. These reported experiences contrast sharply with those of adherent participants who tended to describe training as helpful, enjoyable, and even rewarding. Collectively, these findings highlight how an individual's perception of the training experience may influence the degree to which he or she adheres. Thus, exploring participants' beliefs and attitudes towards training as well as finding ways to optimize their training experiences may result in increased adherence. Also of note, in the present sample a greater number of individuals were considered tolerant of the training program than adherent. What this means is that there were some individuals who appeared to tolerate the program well, however, they could not complete the entire program and/or could not complete it within the recommended time-frame. These findings highlight the importance of tailoring an intervention to individual needs and exploring different intensity schedules (e.g., 3 times per week for 9 weeks), which is an option that may improve adherence for a subset of patients who found the recommended intensity schedule (i.e.. 5 times per week for 5 weeks) too strict. In fact, some recent preliminary research has shown that variations to the original protocol (i.e., shorter individual training sessions in which the number of exercises in each session is reduced as compared to the original protocol but the number of trials is kept the same per exercise, thus resulting in training extending beyond the 5-6 week period) are as effective in leading to improvements as the original protocol (personal communication with Stina Soderqvist, Pearson consultant, 2015; based on results of unpublished report). Furthermore, this preliminary research has found that the shorter training protocols were generally associated with more positive ratings of the training experience. With further research, perhaps shorter protocols will turn out to be optimal for trainees who are less likely to manage training on the original protocol, whether due to time constraints in everyday life or due to limited endurance.

Subjective Experiences

Since, to our knowledge, this was the first time Cogmed was being used with a sample of pediatric-onset MS patients, participants' opinions, attitudes, and subjective experiences with the training program were explored through interview, in order to better capture feasibility and perceived benefit of the training program in this population.

With respect to participant-reported change, all individuals (with the exception of one individual) acknowledged improvements in their WM, manifested as increased ability to hold information online and recall information after short periods of time following manipulation and/or interference. These individuals provided several examples of how the improvements in WM that they had noticed manifested in their everyday functioning at work or school. Subjective reports of change in day-to-day WM functioning in this study are consistent with previous research findings with other pediatric and young adult clinical populations who trained with Cogmed (Johansson & Tornmalm, 2011; Kronenberger et al., 2011).

While such a high degree of *self-reported* change in WM was reported in the current study sample, clinically significant change on *objective,* untrained measures of WM was found to be very limited. Together, these findings call attention to the importance of considering subjective report in conjunction with objective report when examining efficacy of cognitive interventions. If, in the current study, only quantitative methods had been used to investigate efficacy, one would have concluded that cognitive training is not efficacious for pediatric-onset MS patients and may have completely discarded it as a potential avenue for addressing cognitive impairment in this population. While limited efficacy findings in the current study could be reasonably attributed to small sample size, it is also possible that neuropsychological measures alone are not sensitive enough to fully capture the impact of cognitive interventions on people's lives. This highlights the need for future research designs that incorporate multiple approaches to the analysis of efficacy of Cogmed in pediatric-onset MS patients (i.e., neuropsychological performance, subjective report, and brain imaging).

When participants were asked about their overall thoughts about the training program, a number of both positive and negative aspects of the program emerged. Participants described the training program as helpful, rewarding, and enjoyable (both the overall program and particular training exercises, e.g., Spacewhack). Some participants also commented on the value of an intervention such as Cogmed in terms of addressing their concerns about their own cognitive decline. Aware of their cognitive difficulties, these individuals were searching for something that could potentially help with these difficulties. It deserves mention that these individuals who seemed to show awareness of their cognitive difficulties and who seemed to value the training program were also considered to be adherent and tolerant of training. This finding suggests that insight into one's own cognitive difficulties, coupled with a desire for something to target these difficulties, may serve as factors for increasing adherence and tolerance to Cogmed in pediatric-onset MS patients. It is important to acknowledge that such individuals may demonstrate expectancy effects on subjective measures of change. With respect to negative aspects of the program, the most commonly reported negative aspect was how time-consuming the individual training sessions were (i.e., reported in 5 out of 9 individuals). Other negative aspects (reported in 3 or fewer of the 9 individuals) included that the training was repetitive, challenging, tiring, and felt like a chore. Such findings resemble those of previous research in which participants found Cogmed training to be enjoyable yet mentally exhausting and requiring a great deal of effort (Hardy et al., 2013; Johansson & Tornmalm, 2011; Kronenberger et al., 2011). Consistent with previous research (Hardy et al., 2013), most of the participants (8/9) did not report having any technical difficulties with the program or navigating through the program. One non-adherent participant described how he misplaced his computer log-in information which is why he could not complete training. However, direct problems with the Cogmed program itself were not the reason for this participant's inability to complete training.

Almost half of the sample (44%) in the current study acknowledged that the weekly support provided by their Cogmed Coach served as reinforcement for getting through the training. The active management of motivation through the Cogmed coach, together with Cogmed's adaptive component, is a feature of this intervention program that seems to separate it from other self-proclaimed "brain-training" programs. Given how mentally taxing and demanding the Cogmed program is, the role of the Cogmed coach may be likened to that of a *health coach*, who practices health education and health promotion within a coaching context in order to help facilitate the achievement of individuals' health-related goals (Palmer, Tubbs, & Whybrow, 2003). Health coaching has emerged as a part of disease management initiatives, and it has been recommended as an effective method for improving patient adherence to medication regimens (Sacco, Morrison, & Malone, 2004). Cogmed coaching appears to share several aspects of the health coaching approach that has been adopted in previous research for improving medication adherence in diabetic patients (Melko, Terry, Camp, & Healey, 2009), including: having an initial face-to-face session at which an individual receives psycho-education with respect to the intervention (i.e., orientation to WM and the Cogmed program); receiving educational materials to take home (i.e., steps on how to use Cogmed and navigate through the program); defining active steps an individual will take to complete training (i.e., putting together a schedule for when the individual will complete his/her training); regular phone consultations with individuals to assess and reinforce treatment goals (i.e., weekly phone check-ins); and regular monitoring of an individual's progress as well as the provision of strategies for attaining goals (i.e., monitoring online training data and brainstorming with individuals who are struggling to complete training). Interestingly, one-third of the sample acknowledged using intrinsic motivation (either in conjunction with or without coaching support) to get through training. These individuals were deemed as both adherent to and tolerant of the training. This finding contrasts with two individuals, both considered non-adherent, and who described the training as "boring", who acknowledged using external reinforcements during training (i.e., monetary rewards, food, playing video games). The motivational literature has repeatedly shown that extrinsic rewards such as monetary incentives can considerably weaken intrinsic motivation (Deci, Koestner, & Ryan, 1999) and, ultimately, performance (Burton, Lydon, D'Alessandro, & Koestner, 2006). The findings of the current study are in line with previous Cogmed research which found that those individuals who appeared to be more intrinsically motivated (i.e., had self-perceived cognitive deficits, an increased need for cognition, and perseverance for long-term goals) were the ones who successfully completed training (Jaeggi et al., 2013). The findings also suggest that support provided by the Cogmed coach alone is not sufficient to overturn an individual's desire to discontinue with the training program when internal motivation is lacking. Of note, health coaching somewhat differs from Cogmed coaching in that it involves motivational interviewing as a technique to improve an individual's awareness of their situation, accept responsibility for their health outcomes, and explore perceived barriers as well as beliefs and expectations about disease management (Melko et al., 2009). Perhaps incorporating these components into Cogmed coaching could help to improve training adherence in individuals with limitation internal motivation.

It is important to point out that all individuals described no interference of the cognitive training in their social lives, and two-thirds of the sample described no significant impact on their daily routine. This finding is significant because it adds to the feasibility and desirability of implementing an intense intervention such as Cogmed in emerging adults with MS, for whom maintaining their social lives is often important. A home-based rehabilitation program such as Cogmed was chosen in lieu of a clinic-based program for the following reasons: young people often have busy schedules due to competing academic and extra-curricular demands, thus, such a flexible program would allow them to plan training sessions according to their own schedule; young people may have had to rely on parents/guardians for transportation had it been a clinic-based program, and they would need to have been transported five-times a week, which would have been a very demanding commitment; and given that young people today tend to gravitate towards technology and are comfortable with using it, it was thought that a computerized program would appeal to this demographic.

Of note, almost half of the sample (44%) acknowledged that work/school commitments served as an external barrier to training. This finding highlights the importance of ensuring that individuals who undergo Cogmed training are not overwhelmed by other commitments or identifying another time when their academic/employment commitments may be less demanding (i.e., during the summer holidays). A final comment regarding subjective experiences is that participants made suggestions for changes to the training program which included shortening the length of individual sessions, reducing the number of exercises per session, decreasing the repetitiveness of the exercises (e.g., Input Module and Input Module without Lid), and making the program more visually appealing to youth. While some of these suggestions are already being put into practice by the software developers (e.g., shorter training protocol), the other suggestions should be taken into account when developing future cognitive rehabilitation programs, particularly with individuals with pediatric-onset MS, for whom fatigue is a well-known challenge (Amato et al., 2010; Goretti et al., 2012).

Individual Characteristics

Perhaps the most interesting relationship from the present undertaking that deserves further study is the clear positive association that was found between normalized brain volume in individuals with pediatric-onset MS and extent of improvement on Cogmed. Higher normalized brain volume appeared to go hand in hand with increased WM performance from baseline to post-intervention. This finding draws attention to the influence that brain integrity (and neural reserve in general) may have on the degree to which individuals can profit from cognitive rehabilitation efforts that focus on restoring underlying neural mechanisms. The idea that brain atrophy may constrain the capacity for neuroplasticity, with more extensive and irreversible tissue loss being associated with reduced capacity for functional reorganization, has been supported in previous MS research with adults (Hildebrandt et al., 2007; Tomassini et al., 2012b). More specifically, research suggests that cognitive rehabilitation efforts which focus on the *restoration* of complex cognitive functions that involve long-ranged cortical connections, as well as more conscious and flexible control (e.g., working memory), may not be suitable for individuals with a greater degree of brain atrophy since such functions tend to be more vulnerable to the neuropathological effects of MS. Some types of or degrees of brain damage in certain individuals may result in neural circuits which are severely depleted and/or disconnected that rehabilitative efforts aimed at restoration of underlying networks will undoubtedly, allow very limited opportunities for restitutive reconnection (Sohlberg & Mateer, 2001). Such individuals may benefit from efforts aimed to promote the use of *compensatory* strategies and behavioural adaptation. Collectively, previous research and the findings of the current study would suggest that individuals with less severe brain atrophy, and perhaps, adequate capacity for neuroplasticity, may be suitable for a cognitive rehabilitation program such as Cogmed (Robertson & Murre, 1999).

Other clinical characteristics arising from the current study which are likely related to extent of brain volume reduction include age at disease onset, disease duration, and ongoing disease activity (as evidenced by increased number of cumulative relapses). The fact that the individual from the present study who showed the lowest normalized brain volume was also the youngest in the group at disease onset and had the longest disease duration highlights the need for cognitive rehabilitation efforts in the context of degenerative disease that target those who are at greatest risk of decline (i.e., individuals who develop MS early on) to see if cognitive functioning can be preserved. Beyond the effect on cognitive dysfunction, cognitive interventions may have the potential to expand neural reserve, which may be crucial for pediatric-onset MS patients in order to delay cognitive decline. Recent MS research has shown that *cognitive* reserve (i.e., lifetime cognitively-enriching experiences, e.g., cognitive training) independently protects against disease-related cognitive decline (particularly memory) over and above *brain* reserve via superior/optimal neurocognitive processing (Sumowski et al., 2013).

Another area which emerged as one that warrants further study is the association between IQ and improvement on Cogmed. The individual who showed the largest improvement on Cogmed trained WM tasks also had the highest baseline IQ score. This finding is consistent with previous research that has found moderately-sized correlations between baseline estimated IQ scores and magnitude of change in performance-based outcomes following training such that individuals with higher baseline IQ scores tend to show greater improvements in visual WM following training (Hardy et al., 2013). This finding needs to be explored further to determine whether improvements could be the result of increased cognitive reserve prior to starting training and/or some other contributing factor.

Finally, the Motivation for Change Questionnaire (MCQ) did not appear to predict performance on Cogmed, nor adherence or tolerance, in this group of individuals with pediatric-onset MS. There could be a number of reasons as to why this was the case. Upon closer examination of the individual items on the MCQ, it becomes apparent that they do not tap into intrinsic and extrinsic motivation. Given the relationship that seemed to emerge across participants in this study between presence of intrinsic motivation and training outcomes, it becomes evident that the MCQ is not well-equipped to discriminate between individuals on this aspect of motivation. Another plausible reason for why the MCQ results did not predict training outcomes is that the individual items pertained to one's *overall* life and were not specific to one's motivation to undergo cognitive training. The generality of the questions can make responding challenging because individuals may have varying levels of motivation for different aspects of their lives. For example, if an individual is highly motivated to get better grades in school, but poorly motivated to exercise more regularly, how would he/she comment on his/her overall motivation in life? Another consideration is the fact that participants in the current study completed the MCQ at baseline testing, prior to commencing the intervention. At this time, moderate-to-high levels of motivation (as reflected by moderate-to-high scores on the MCQ) could have reflected eager and enthusiastic individuals who had not yet experienced the intensity of the cognitive training that would ensue. It would have been interesting to assess participants' level of motivation post-training to see if training had any impact. Based on the results of the current study, it would be interesting to see whether an alternate measure of motivation – more specifically, something that assesses an individual's degree of intrinsic versus extrinsic motivation (and perhaps, specifically with respect to cognitive training) – might better predict performance, adherence, and tolerance in this patient population.

Previous research has found that individuals who signed up for cognitive rehabilitation reported more cognitive failures than those who signed up to just complete a baseline assessment (Jaeggi et al., 2013). These authors suggested that the participants who signed up for training had some sort of self-perceived deficit that might have influenced their interest in improving their WM as well as cognitive performance in the first place. On top of this, the authors found that individuals with the highest IQ scores combined with the highest need-for-cognition scores (as assessed through a questionnaire, 'Need for Cognition', Cacioppo & Petty, 1982) were the individuals who successfully completed training. Thus, it appears that a combination of high intelligence coupled with awareness of cognitive difficulties and a need for increased cognition seems to make up the type of individual who is motivated and shows consistent engagement to complete a training study. It will be important to use such measures in future research studies (i.e., Need for Cognition, Cognitive Failures) to get an idea of how intrinsically motivated a potential candidate for cognitive rehabilitation may be. The newest version of Cogmed (version 3.0) includes a motivation/expectations questionnaire that allows the Training Coach to detect low levels of motivation and to initiate appropriate coaching and/or encouragement, as a result. It consists of eight questions and is completed prior to training, halfway through training, and immediately post-training. This questionnaire, though not yet validated, could be used as a starting point to begin to investigate how motivation may influence training outcomes, but it would need to be followed-up with more detailed questions as to an individual's response. For example, one of the items asks an individual to indicate whether he/she agrees or disagrees with whether he/she thinks that the training will be helpful. Based on an individual's response to this item, it would be important to ask follow-up questions (e.g., "*How* will the training help you?").

Performance on Trained and Non-Trained WM Tasks

Each participant in the present study showed improved performance on trained Cogmed verbal and visuo-spatial WM exercises, and this is consistent with previous research studies using Cogmed in clinical populations (Klingberg et al., 2002; Klingberg et al., 2005; Kronenberger et al., 2011; Westerberg et al., 2007). As a group, observed changes in verbal WM performance were larger than changes in visuo-spatial WM performance. Given that three-quarters of the

Cogmed exercises train visual-spatial ability, this finding in the current study may seem counterintuitive. However, this finding is in keeping with the results of a recent meta-analysis of computerized WM training programs, including Cogmed (Melby-Lervåg & Hulme, 2013), which found largely-sized immediate gains on verbal WM tasks in comparison to moderately-sized immediate gains on visual-spatial WM tasks. A possible reason for the difference in the current study could be that the individuals in the study sample had more difficulty with visual-spatial WM as opposed to verbal WM. Upon examining the group's baseline performance on objective visual-spatial WM tasks, as a group, they are performing almost one standard deviation lower (Finger Windows mean, z = -0.93) in comparison to the verbal WM tasks (Auditory Working Memory mean, z = 0.18; Numbers Reversed mean, z = 0.05), though direct comparison between these different measures is limited by the use of different normative groups in deriving the neuropsychological scores. While this hypothesis serves as a plausible explanation for the observed discrepancy between visual-spatial and verbal WM gains, it will be important to see whether a similar pattern is replicated in larger randomized control studies. Furthermore, it is important to keep in mind the limited interpretability of seemingly improved verbal performance than visual-spatial performance on trained WM exercises given that effect sizes could not be meaningfully calculated (i.e., the measures of visuo-spatial and verbal WM were obtained by taking the mean of performance on individual exercises). Given this limitation, it is hard to comment on whether such observed "gains" are clinically meaningful at this point in time.

Upon examining performance on *non-trained* measures of WM, clinically significant improvement was only observed on a measure of visual-spatial WM (Finger Windows, 1/8 individuals), verbal WM (Numbers Reversed, 1/7 individuals), and a more complex measure of verbal WM (Auditory Working Memory, 2/8 individuals). In contrast, no changes were observed on the non-working memory (control) measures. It is noteworthy that the one individual who showed clinically significant improvement on two non-trained measures of WM also showed the greatest magnitude of change on the trained Cogmed WM exercises (i.e., COG_09). Moreover, this participant acknowledged striving to challenge himself during training (i.e., improving his Cogmed performance by striving to beat his daily high scores) and removing electronic distractions when training (i.e., turning his cell phone off), and he was the only participant to recommend *not* decreasing the intensity of the training program for he felt that it would need to be this intensive in order to be effective. Collectively, these preliminary observations seem to suggest that individuals who like to challenge themselves, who take active steps to maximize their training benefits, and who can appreciate the need for an intensive program may show favourable training outcomes.

Limitations and Future Directions

An obvious limitation of the current study was the small sample size. With nine individuals, the generalizability of the findings must clearly be applied with caution to all individuals with pediatric-onset MS until the results have been replicated in larger studies. Additionally, a larger sample size is needed to examine the effects of demographic and clinical variables on intervention efficacy with adequate power. However, the purpose of the present study was to introduce a WM training program that was completely novel to the MS population and to ascertain some idea of its feasibility and efficacy, as well as how young patients with MS experience training, before deciding whether to pursue this research further in larger studies. It may have been imprudent to start off with such a large sample without having any idea of how individuals with pediatric-onset MS would even respond to Cogmed training. Furthermore, this study provided valuable information by identifying some individual characteristics which may result in increased adherence and tolerance with training, as well as positive responses to training and fairly positive experiences. With this information in hand, one can utilize it to screen for suitable candidates with pediatric-onset MS for cognitive training and potentially avoid the financial and personal costs of including individuals least likely to complete and/or benefit from such training. This study served as a "start point" to provide direction and next steps for research pertaining to treating cognitive impairments for individuals with pediatric-onset MS.

A second limitation of the current study was the absence of a no-treatment or alternate treatment comparison group. Without a control group, it makes it harder to ascribe the achieved gains in WM to the Cogmed training program or to some other factor such as practice effects. However, it should be pointed out that while the present study did not include control "participants", it included control "measures". A few individuals showed clinically significant improvement on select non-trained measures of WM, yet none of the participants showed change on neuropsychological tests that do not involve WM, from baseline to post-assessment. This pattern of 'no change' on tasks that do not measure WM helps to rule out between-session factors (e.g., time of day of testing, practice effects) as having contributed to the observed training outcomes. It will be important to replicate this pattern of results in future, randomized controlled studies. Thus, it would be prudent to include non-WM measures as well as WM ones in such studies, to investigate the specificity of Cogmed training. Given the ethical ramifications of withholding a potentially efficacious treatment (i.e., cognitive rehabilitation) from cognitively-vulnerable individuals, such as those with MS, perhaps an ideal control group for future research would be a wait-list control group.

Another limitation of the current study was that sustainability of the findings over time was not investigated. Previous studies have shown even greater effects of Cogmed in the long-term (i.e., 3 or 6 months post-intervention compared to what is observed immediately post-intervention) through consolidation of WM gains in day-to-day life experiences. Future studies that include longitudinal follow-up at these time points are required to address this limitation and to have a better understanding of the stability and sustainability of results of Cogmed training over time. In the case of pediatric-onset MS, it is important to remember that we are dealing with a population that has poor long-term prognosis, hence, the goal will not only be to repair an injured system, but to also preserve its functioning over time. On a related note, ultimately, rehabilitation needs to improve an individual's quality of life, hence, gains that are confined to a very specific skill that do not transfer more generally may be limited in their overall usefulness. Once near-transfer effects are replicated in future studies, the next step will be to demonstrate training effects that extend to other areas of an individual's functioning (e.g., academic functioning).

Another limitation of the current study was the absence of pre- and post-training brain imaging data. Without this information, it is difficult to ascertain whether differences in training outcomes observed in our study may be attributed to variability in individual capacity for neuroplasticity. With the advent of neuroimaging techniques that serve to illuminate structural and functional connectivity of neural networks, future research studies that combine behavioural and neuroimaging techniques will provide the basis for scientifically-informed neurorehabilitation in pediatric-onset MS. Such techniques are particularly important for this population, given that the disease is occurring in the context of developing neural networks. Rather than relying on purely behaviour-centered research, complex, multimodal approaches to the study of cognitive rehabilitation in this population will provide a richer understanding of neural mechanisms underlying training outcomes, and perhaps eventually lead to the identification of imaging markers to measure the effects of cognitive training.

With respect to the collection of qualitative data in this study, some potential limitations should be pointed out. Since all exit interviews were conducted by this writer who in some instances served as the Training coach for some of the participants, concern could arise over having the interviewer also be the coach and whether this could have influenced the qualitative findings. Though such concern is warranted, safeguards were put in place in an attempt to minimize potential bias, which included: discussion of biases and expected findings with the supervising psychologist (C. Till) who did not attend the interviews nor participate in coaching, the use of a standard list of questions that was administered to every participant, audio recording of participant responses, transcription of interviews verbatim (and by another person) prior to any type of analysis, and having a different person (RA) serve as coach from the interviewer when possible. Future research studies should endeavour to assign separate personnel to participants for coaching than for conducting exit interviews, in order to eliminate potential biases. Future research studies should also strive to include multiple coders, in order to implement cross-checking of coding strategies and interpretation of data by independent researchers.

Another potential limitation to the qualitative analysis of data in this study is that, while the use of counting procedures (i.e., counting the number of individuals who endorsed the same theme) can provide a sense of the most common/salient themes, it is possible that pure frequency counts of words may result in some themes being overlooked or seeming less salient because participants might have used a different term for the same word. However, it deserves mention that this limitation was addressed in the current study, in part, by modifying word frequency queries in the analysis software before running them so as to include synonyms of words too. For example, if the goal was to examine how many participants used the word "tiring" when describing training, by modifying search criteria, words used by participants such as "exhausting" or "fatiguing" would also be identified by the software as relating to the theme of "tiring".

Potential Implications for Practice

Based on the findings of this study, recommendations for practice were developed that researchers and clinicians may find useful when selecting candidates with pediatric-onset MS to undergo intensive computerized cognitive training. Although these recommendations are based on a small, uncontrolled study of one cognitive program, and thus should be considered preliminary and in need of further research, we hope that they will serve as guide for professionals in the interim. **Table 7** offers a quick reference to the recommendations.

1) Consider age and disease duration. It will be important to consider age, disease duration, and other clinical characteristics that may influence an individual's response to cognitive training. In the current study, the patient who showed the smallest gains after cognitive training was also the youngest at disease onset (i.e., 7.6 years of age) and had the longest disease duration in the group (i.e., 10.3 years), whereas the individual who showed the largest gains after training was the oldest at disease onset (i.e., 18.5 years) and had the disease for less than half the time as the other individual (i.e., 4.2 years). Factors such as age at disease onset and disease duration could interact with or contribute to brain integrity, thus influencing one's capacity for neuroplasticity, and in turn, response to cognitive training.

2) Consider degree of brain atrophy. Given the positive association that emerged in the current study between normalized brain volume and improvement on Cogmed, it will be important to consider the degree of brain atrophy in potential and/or selected participants. Knowledge of underlying brain integrity will help direct a clinician in deciding whether an individual may be beyond the point of retraining a network. It the network is too damaged, then compensatory strategies may be far more effective for this individual. Perhaps those with highly compromised brain integrity may not benefit from cognitive training that focuses on restoring damaged networks as much as someone with more moderate levels of impairment.

3) Screen for motivation. The importance of paying attention to motivational factors that can affect a participant's expectations and coping strategies, as well as training outcomes, during a rehabilitation program has been emphasized in the current study. The results of the current study suggest that assessing how intrinsically versus extrinsically motivated a potential candidate is may be more informative than assessing motivation for change in one's life situation. That is, individuals who are more intrinsically motivated may be more likely to persist with, adhere to, and tolerate such a demanding training program. It might be helpful to use a measure such as the Intrinsic Motivation Inventory (IMI; Ryan, Mims, & Koestner, 1983) to assess an individual's degree of intrinsic motivation. This instrument assesses an individual's interest/enjoyment, perceived competence, effort, value/usefulness, felt pressure and tension, and perceived choice while performing a given activity, yielding six subscale scores. In addition to administering this questionnaire, one could inquire about the types of rewards that candidates usually use or have used in the past when they have/have had to complete a project or some other demanding task. This information could help to identify those who are most motivated for training. One could also use the brief expectations/motivation questionnaire that is included in Cogmed version 3.0, as it does contain some items which seem to relate to intrinsic motivation. Follow-up questions about an individual's responses on this questionnaire would need to be asked, to provide some context.

4) Screen to identify level of interest/need for cognitive rehabilitation. Given the findings of the current study which suggest that individuals who are aware of their cognitive difficulties and who are seeking opportunities to improve their cognition might be the most motivated to successfully complete intensive cognitive training, professionals should consider screening potential candidates for such qualities. In doing so, one can determine the level of need as well as interest there is on the part of the participant for undertaking an intensive training program. Professionals may consider using questionnaires such as the 'Need for Cognition' (Cacioppo & Petty, 1982) and Cognitive Failure Questionnaire–Memory and Attention Lapses (CFQ-MAL, as used in McVay & Kane, 2009). It may be helpful to supplement this with a brief, informal interview with potential participants prior to commencing training. Such screening might help to identify those who would benefit the most from training and who may also be the most adherent and tolerant of an intensive training program.

5) Explore individual beliefs and attitudes towards training. Prior to commencing the training program and also during training, it might be useful to explore an individual's beliefs and attitudes towards training so as to identify individuals who may have a negative or lackluster attitude. It is these individuals who may experience considerable challenge with adherence and tolerance. By identifying such individuals, the training coach may be able to strategize to optimize the training experience for these individuals.

6) Use a training coach. Consider including a training coach who can remotely view participants' data, monitor their progress, and make weekly contact with participants. If the training coach notices anything unusual in terms of training or that a participant is not training, they can follow up with them and try to resolve any technical difficulties or help participants strategize about how to overcome barriers to training. The training coach can also check in with participants to see how engaged they are with training, and obtain an estimate of the effort and attention put forth by participants towards training, in order to provide some context for the data. As demonstrated by this study, the motivation provided by a training coach may serve as a form of social reinforcement for participants, in order to help them get through training successfully. The coach's active management of motivation is one of the features of Cogmed that make it different from other types of cognitive training. It would be interesting to see if the role of the training coach could be expanded upon to incorporate components of motivational interviewing, particularly for those participants who have limited motivation to do training.

7) Tailor intervention to individual needs. An individual deemed as lacking motivation to do training (e.g., may not be aware of cognitive difficulties or may have negative attitudes towards training) is likely to encounter challenges with intensive training. Options for such individuals include considering the use of different intensity schedules or providing individuals with strategies of a compensatory nature for their cognitive difficulties. If one can help a potential candidate realize the need and benefit of such cognitive training, without making him/her feel coerced, this may also be something to consider before deeming him/her as unsuitable for cognitive retraining.

8) Ensure that cognitive training is undertaken at an optimal time. As reported by participants in the current study, competing academic and/or employment demands may serve as barriers to cognitive training, and could influence one's adherence with training. When considering a potential candidate, it would be useful to ascertain his/her involvement in other activities that could interfere with finding time and energy to train. If a candidate appears suitable for training in all other aspects except for having competing demands, it may be prudent to postpone cognitive training to a later time when demands are lower. For example, if the individual is a student, perhaps the summertime may be a more appropriate time to undertake cognitive training when classes are done.

Conclusion

To date, research has focused on the identification and characterization of cognitive impairment in pediatric-onset MS. While cognitive difficulties are the most disabling deficit accompanying the early stages of pediatric-onset MS, there is currently no established effective treatment for cognitive dysfunction. The current study demonstrated the feasibility of implementing computerized training in pediatric-onset MS patients with cognitive impairment, something that has never been done before with this population. This study also helped to elucidate which individual and disease-related factors may influence feasibility and the benefit of cognitive training in pediatric-onset MS. Though the current study by itself cannot say with confidence at this moment that Cogmed can serve as an efficacious treatment for cognitive impairment in individuals with pediatric-onset MS, preliminary evidence of potential improvement with a subset of pediatric-onset MS patients was obtained, using a triangulated approach to assessment. Now that the current study has demonstrated feasibility with a small sample of pediatric-onset MS patients and called attention to the nuances of individual training responses, the logical next step is a path towards research in this area that aims to address current methodological limitations, in order to truly unravel the effects of cognitive training on cognitive functioning in this vulnerable population.

Table 1. Demographic and clinical characteristics of participants (N = 9).

Study ID	Sex	SES	Estimated IQ[a]	MCQ[b]	Age at baseline (years)	Age at disease onset (years)	Disease duration (years)	Number of cumulative relapses	EDSS score	Disease-modifying therapies	Normalized brain volume[d]	T1 lesion volume (mm^3)[e]	T2 lesion volume (mm^3)[e]
COG_02	F	10.5	102	21	16.5	15.7	0.9	2	1.0	None	-0.66	0.00	1.69
COG_05	F	49.0	122	19	22.9	16.7	6.2	6	5.0	Tysabri	-0.15	3.30	3.54
COG_06	F	28.0	89	27	14.2	12.0	2.2	1	1.5	Copaxone	-0.53	3.17	3.61
COG_07	F	45.5	113	24	20.0	14.3	5.8	7	1.5	Gilenya	0.39	3.40	3.58
COG_08	M	43.0	91	27	24.7	17.1	7.6	2	1.5	None	-1.17	2.49	2.88
COG_09	M	37.5	118	27	22.7	18.5	4.2	Unknown	4.0	Copaxone	0.19	3.57	3.70
COG_10	M	28.5	78	26	14.6	12.6	2.0	1	1.5	Avonex	-1.15	3.31	3.59
COG_12	F	61.0	103	26	16.0	14.2	1.9	5	2.5	Avonex	-0.74	4.04	4.37
COG_15	F	46.5	98	26	17.8	7.6	10.3	13	3.0	IVIG, Rituximab	-1.74	2.34	2.50

Mean	**-**	**38.8**	**101.6**	**24.8**	**18.8**	**14.3**	**4.5**	**3.5** [c]	**1.5**[c]	**-**	**-0.62**	**2.85**	**3.27**
SD	**-**	**14.8**	**14.4**	**2.9**	**3.9**	**3.3**	**3.1**	**4.1**	**1.4**	**-**	**0.69**	**1.19**	**0.79**
Range	**-**	**10.5-61.0**	**78-122**	**19-27**	**14.2-24.7**	**7.6-18.5**	**0.9-10.3**	**1-13**	**1.0-5.0**	**-**	**-1.74-0.39**	**0.0-4.0**	**1.7-4.4**

[a]IQ as measured by the Wechsler Abbreviated Scale of Intelligence (WASI) 2-Subtest Full Scale IQ.

[b] Motivation for Change Questionnaire; maximum score possible is 28.

[c] Median value is reported.

[d]Z-scores, relative to age and sex-normed values, are reported.

[e]Log-transformed values are reported (due to non-normal distributions).

Table 2. Description of Cogmed-specific outcomes used in the study.

Outcome	**Description**
Sessions	Total number of sessions trained.
Calendar Days	Length of training period in calendar days.
Mean Active Time per Day	Mean number of minutes across the training period spent on active training.
Mean Pause Time per Day	Mean number of minutes across the training period spent on breaks.
Exercise-Specific Performance Improvement Values	Calculated by subtracting the mean training level on the third day for an exercise from the mean training level for a participant's best performance in the final five days of that exercise.
Visuo-Spatial WM Performance Improvement	Calculated by taking the mean of the performance improvement values for all eight visuo-spatial WM exercises.
Verbal WM Performance Improvement	Calculated by taking the mean of the performance improvement values for three verbal WM exercises.
Adherence	Completion of at least 80% (i.e., 20 sessions) of the required sessions within 40 calendar days or less.

Training tolerance	Ratio of time spent on active training to time spent on breaks is greater than or equal to 2:1.

Table 3. Overall program training outcomes of participants (N=9).

Study ID	**Number of sessions trained**	**Length of training period (calendar days)**	**Number of Coach phone calls**	**Mean active time per day (minutes)**	**Mean pause time per day (minutes)**	**Adherent?**	**Tolerant?**
COG_02	25	50	6	44.05	2.55	Yes	Yes
COG_05	25	46	5	49.38	2.03	Yes	Yes
COG_06	25	34	3	51.89	8.43	Yes	Yes
COG_07	5	5	1	41.54	2.45	No	Yes
COG_08	25	41	6	38.32	6.18	Yes	Yes
COG_09	25	39	5	47.39	6.83	Yes	Yes
COG_10	20	135	3	54.40	34.92	No	No
COG_12	24	140	3	38.52	6.77	No	Yes
COG_15	25	34	5	42.78	7.40	Yes	Yes
Mean	**22.1**	**41.0***	**4.1**	**45.4**	**6.8***	**6/9****	**8/9****
SD	**6.6**	**46.7**	**1.7**	**5.7**	**10.1**	**-**	**-**

Range	**5-25**	**5-142**	**1-6**	**38.3-54.4**	**2.0-34.9**	**-**	**-**

*Median value is reported.

**Proportion is reported.

Table 4. Demographic, clinical, neuropsychological, training, and experience-related outcomes of participants (N = 9).

OUTCOME	**COG_15**	**COG_08**	**COG_10**	**COG_05**	**COG_12**	**COG_02**	**COG_06**	**COG_09**	**COG_07**
Verbal WM improvement	0.43	1.38	1.86	2.14	2.27	2.58	2.72	5.69	-
Demographic & Clinical									
Sex	Female	Male	Male	Female	Female	Female	Female	Male	Female
Age at baseline (years)	17.8	24.7	14.6	22.9	16.0	16.5	14.2	22.7	20.0
Age at disease onset (years)	7.6	17.1	12.6	16.7	14.2	15.7	12.0	18.5	14.3
Disease duration (years)	10.3	7.6	2.0	6.2	1.9	0.9	2.2	4.2	5.8
Number of cumulative relapses	13	2	1	6	5	2	1	Unknown	7
Normalized brain volume	-1.74	-1.17	-1.15	-0.15	-0.74	-0.66	-0.53	0.19	0.39
T1 lesion volume (mm^3)	2.34	2.49	3.31	3.30	4.04	0.00	3.17	3.57	3.40
T2 lesion volume (mm^3)	2.50	2.88	3.59	3.54	4.37	1.69	3.61	3.70	3.58
IQ	98	91	78	122	103	102	89	118	113
Motivation for Change	26	27	26	19	26	21	27	27	24
MSNQ-Patient raw score	20	19	20	Unavailable	23	26	2	35	8

Neuropsychological									
WM index change (z-score)	0.96	1.08*	0.33	1.01	0.72	0.57	0.21	0.85	-
Training									
Adherence	Adherent	Adherent	Non-adher.	Adherent	Non-adher.	Adherent	Adherent	Adherent	Non-adher.
Tolerance	Tolerant	Tolerant	Not toleran.	Tolerant	Tolerant	Tolerant	Tolerant	Tolerant	Tolerant
Number of sessions	25	25	20	25	24	25	25	25	5
Length of training period (calendar days)	34	41	135	46	140	50	34	39	5
Mean active time per day (minutes)	42.78	38.32	54.40	49.05	38.52	44.05	51.89	47.39	41.54
Visual WM improvement	1.15	1.33	0.18	1.19	1.14	1.58	0.58	1.24	-

Outcome	COG_15	COG_08	COG_10	COG_05	COG_12	COG_02	COG_06	COG_09	COG_07
Descriptions of training									
Helpful	√	√	√	√	√	√	√	√	
Enjoyed		√	√	√		√			
Overall rehabilitation Program valuable				√				√	
Time-consuming			√		√	√		√	√
Repetitive							√	√	√
Feels like a chore				√				√	
Boring			√		√				
Participant-reported changes									
WM	√	√	√	√	√	√	√	√	
Learning			√		√	√	√	√	

Speed of processing				√	√				
Strategies	√							√	
Attention				√					
Socio-emotional functioning				√		√			
Barriers to training									
School/work/extra-curricular activities			√	√	√	√	√		
Low motivation		√		√	√			√	
Supports									
Coaching		√			√			√	√
Praise from family/friends	√		√	√			√		
Extrinsic rewards		√	√	√	√	√	√		
Intrinsic motivation						√	√	√	

*Based on two subtests because the third subtest was not administered at the pre-training assessment, in error.

Table 5. Exercise-specific, and overall visuo-spatial WM and verbal WM performance improvement values of participants (N = 8).

	VISUO-SPATIAL WM									VERBAL WM			
Study ID	Visual Data Link	Sorter	Rotating Dots	Rotating Data Link	Data Room	Asteroids	3D Cube	Space Whack	***Visuo-Spatial WM*** [a]	Stabilizer	Input Module	Input Module with Lid	***Verbal WM*** [b]
COG_02	2.00	2.47	1.18	1.64	1.00	1.66	1.85	0.81	***1.58***	3.69	2.48	1.56	***2.58***
COG_05	1.93	0.28	1.88	1.55	1.42	0.99	0.21	1.24	***1.19***	1.94	2.06	2.41	***2.14***
COG_06	1.60	0.50	1.64	1.91	0.12	-0.55	-0.47	-0.11	***0.58***	0.55	4.04	3.56	***2.72***
COG_08	2.21	1.80	1.84	0.80	1.18	0.60	0.93	1.28	***1.33***	1.00	1.73	1.42	***1.38***
COG_09	1.62	1.34	1.41	2.53	0.71	1.12	0.02	1.15	***1.24***	5.23	7.01	4.84	***5.69***
COG_10	-0.39	0.94	0.18	0.33	0.82	-.42	0.00	0.00	***0.18***	0.26	2.30	3.03	***1.86***
COG_12	1.07	1.29	1.28	0.88	0.63	1.08	1.96	0.90	***1.14***	1.75	2.99	2.08	***2.27***
COG_15	1.70	1.24	1.62	1.33	1.88	0.30	0.49	0.65	***1.15***	-0.52	0.67	1.13	***0.43***
Mean	**1.47**	**1.23**	**1.38**	**1.37**	**0.97**	**0.60**	**0.62**	**0.74**	***1.05***	**1.74**	**2.91**	**2.50**	***2.38***
SD	**0.82**	**0.70**	**0.54**	**0.70**	**0.54**	**0.78**	**0.89**	**0.54**	***0.45***	**1.90**	**1.92**	**1.25**	***1.53***

Range	**-0.39- 2.21**	**0.28- 2.47**	**0.18- 1.88**	**0.33- 2.53**	**0.12- 1.88**	**-0.55- 1.66**	**-0.47- 1.96**	**-0.11- 1.28**	***0.18-1.58***	**-0.52- 5.23**	**0.67- 7.01**	**1.13- 4.84**	***0.43*- *5.69***

[a]Calculated by taking the mean of all eight visuo-spatial WM exercises.

[b]Calculated by taking the mean of all three verbal WM exercises.

Table 6. Number of individuals showing significant cognitive change using the Reliable Change Index (RCI) method.

Domain/test	**Number improved (N = 8)***	**Number showing no change (N = 8)***	**Number declined (N = 8)***
(Non-trained) Working Memory			
WRAML: Finger Windows	1	7	0
WJ: Auditory Working Memory [a]	2	6	0
WJ: Numbers Reversed [a,b]	1	6	0
Non-Working-Memory			
Doors and People: The Names Test[c]	-	-	-
Benton Judgment of Line Orientation	0	7	1
WJ: Decision Speed	0	8	0

*Data is based on eight participants because post-training data was not collected from one participant who dropped out of the study after five days of training.

[a]Split-test reliability coefficient was used because test-reliability coefficient was not available for this subtest.

[b]Data is based on seven participants because this test was not administered at baseline to one participant, in error.

[c]No reliability information was available for this subtest.

Table 7. Potential recommendations to consider when selecting candidates with pediatric-onset MS to undergo intensive computerized cognitive training.

•Consider age and disease duration
•Consider degree of brain atrophy
•Screen for motivation
•Screen to identify level of interest/need for cognitive rehabilitation
•Explore individual beliefs and attitudes towards training
•Use a training coach
•Tailor intervention to individual needs
•Ensure that cognitive training is undertaken at an optimal time

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Figure 1. Four subtypes of multiple sclerosis (Lublin et al., 2014).

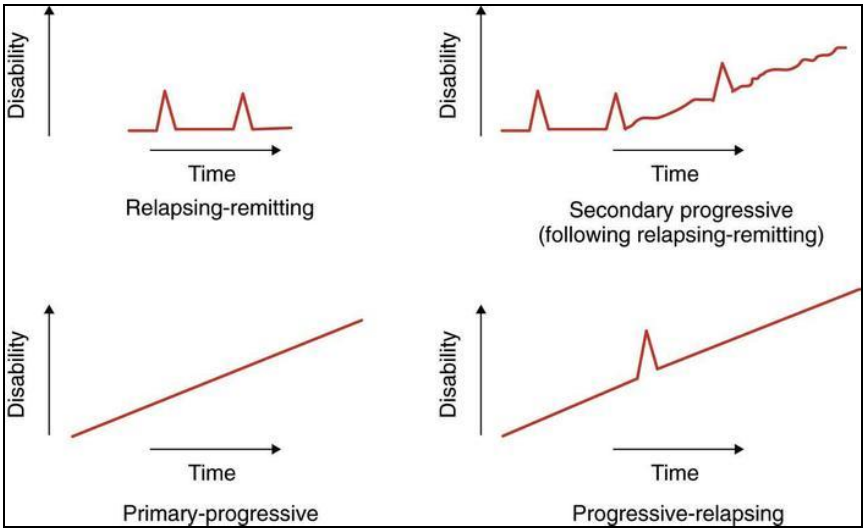


Figure 2. Three-component model of working memory proposed by Baddeley & Hitch (1974).

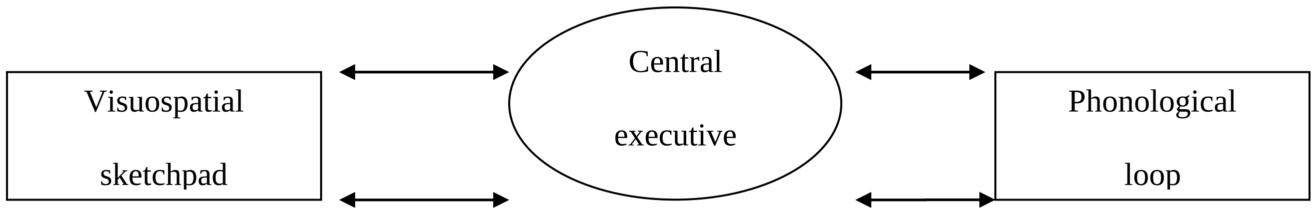


Figure 3. Consort diagram showing patient flow through study.

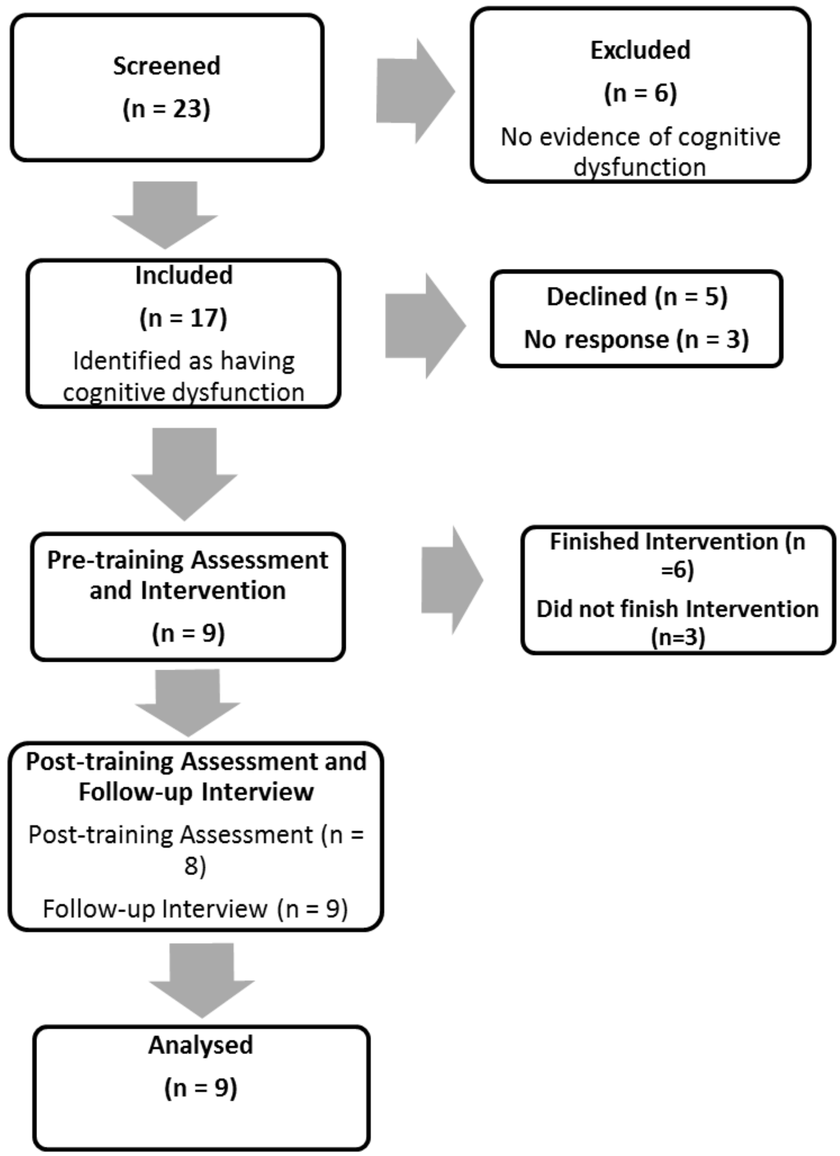


Figure 4 (a). Positive aspects of training program reported by participants.

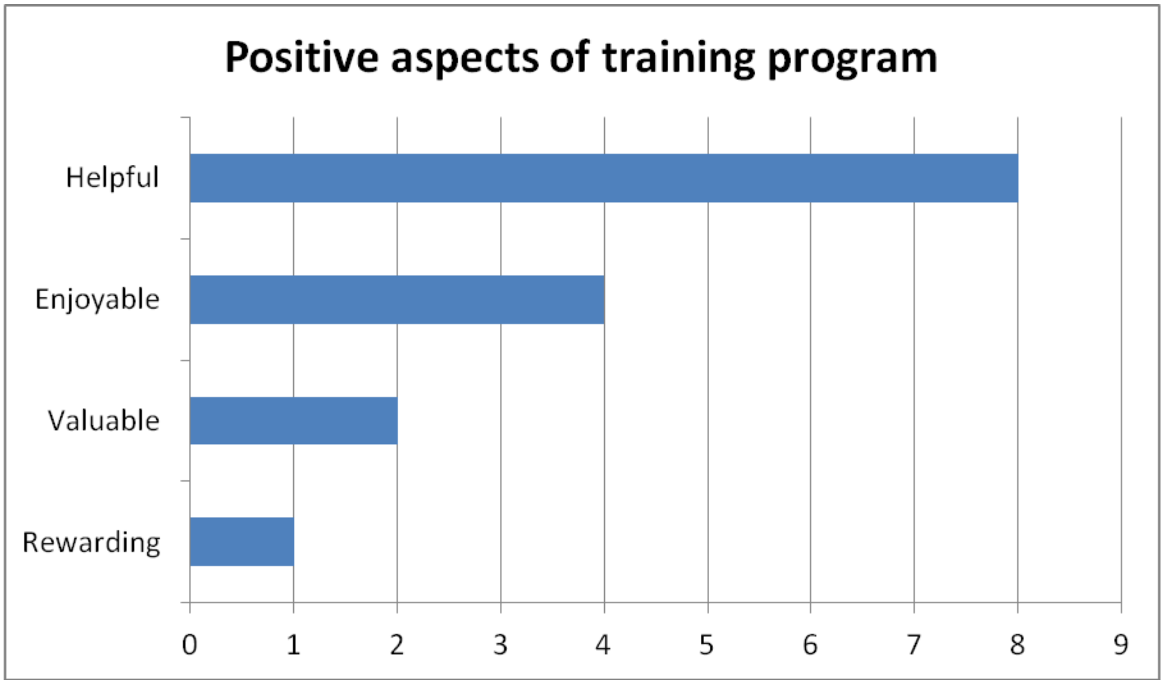


Figure 4 (b). Negative aspects of training program reported by participants.

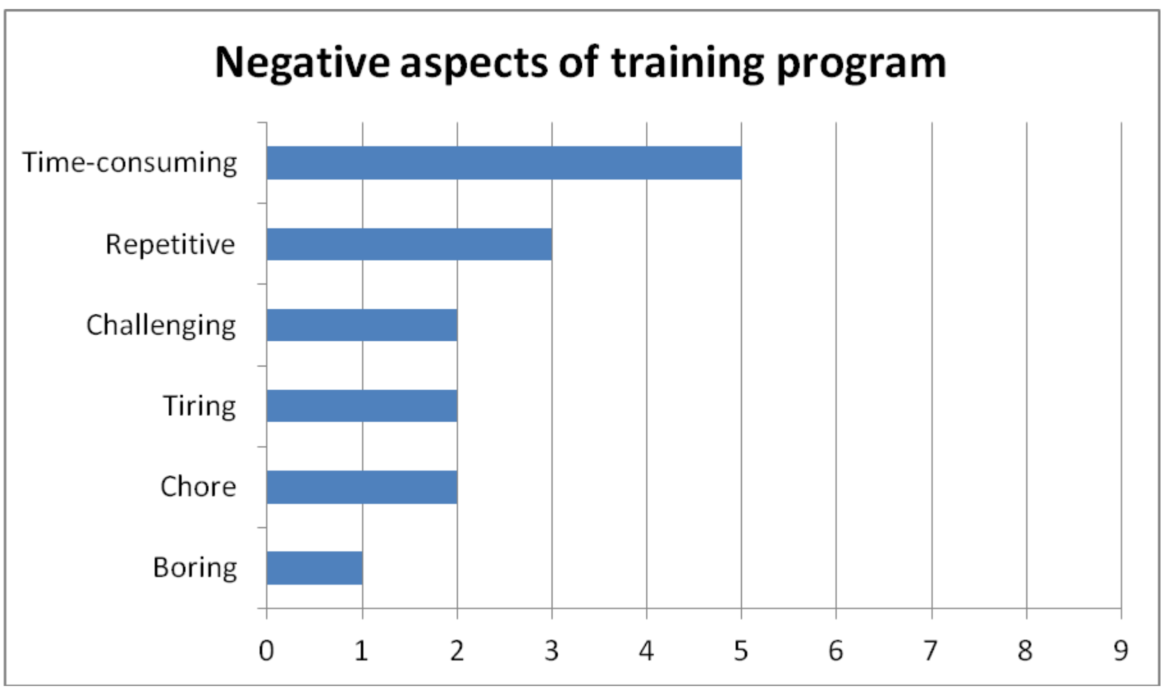


Figure 4 (c). Domains of participant reported changes since doing training.

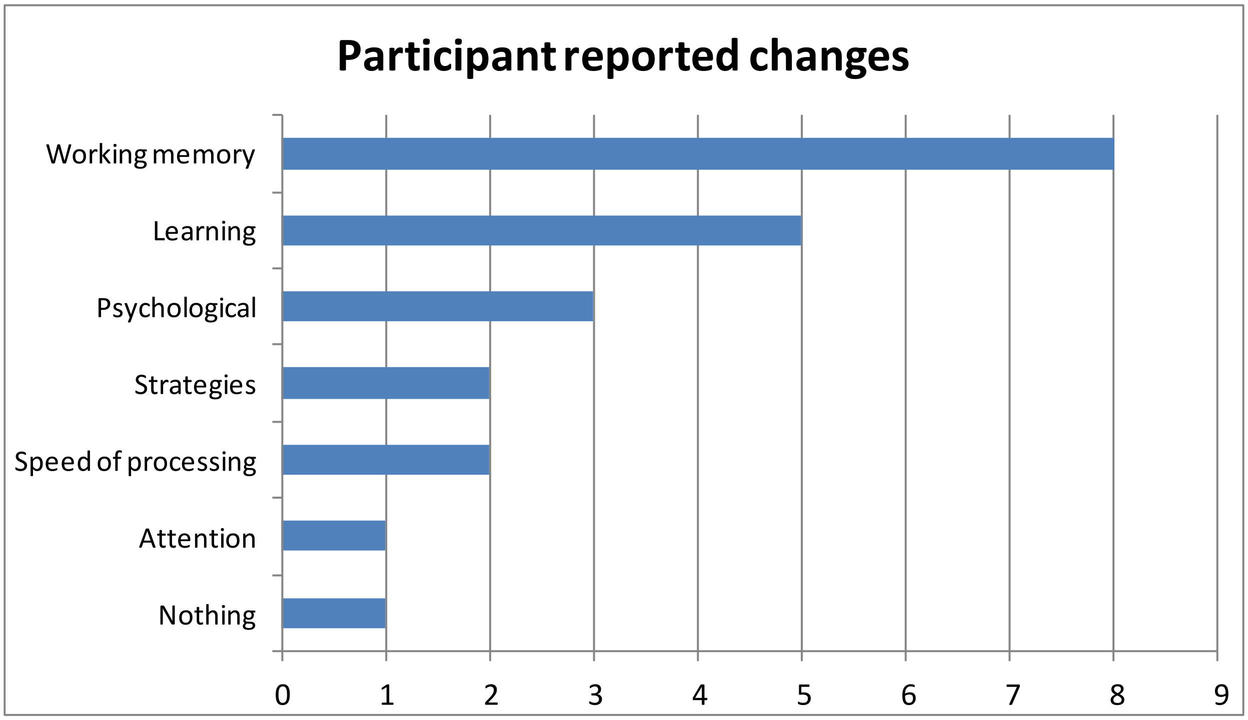


Figure 4 (d). **Participant reported barriers to doing training.**

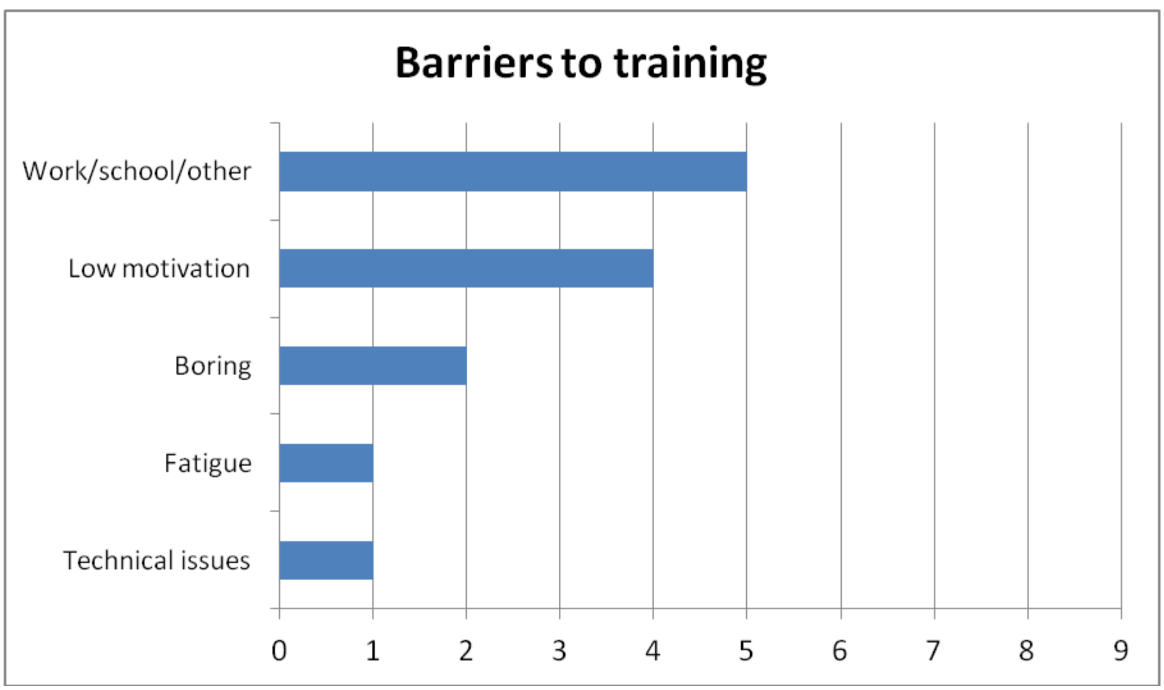


Figure 4 (e). Participant reported supports/reinforcements used for training.

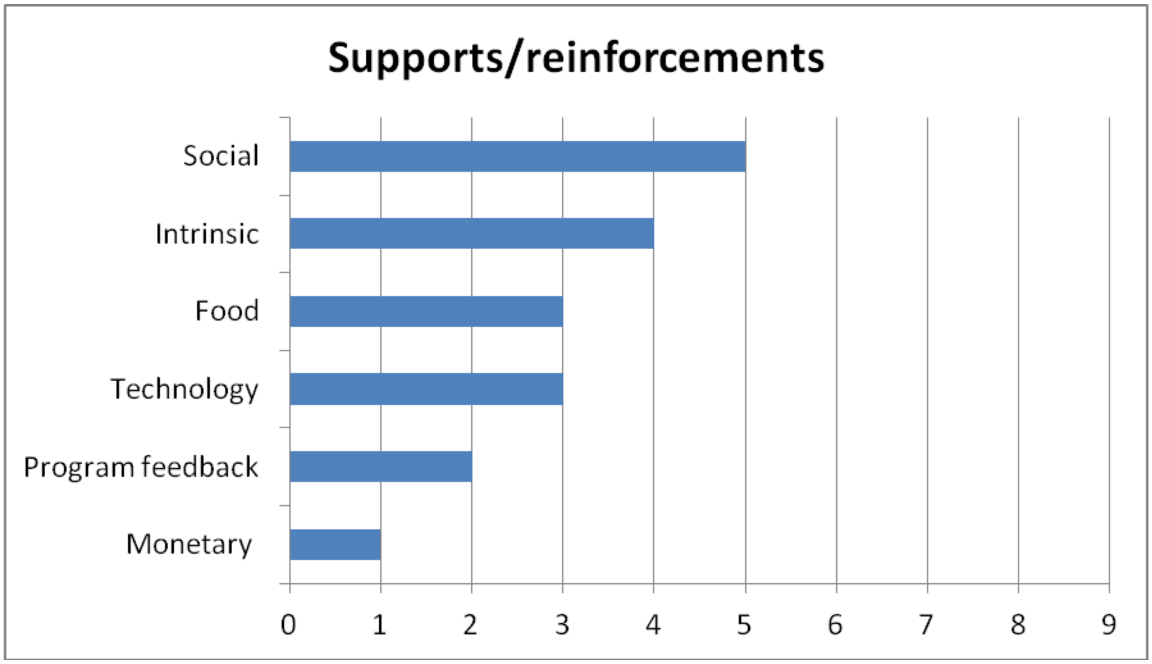


Figure 4 (f). Participant reported distractions during training.

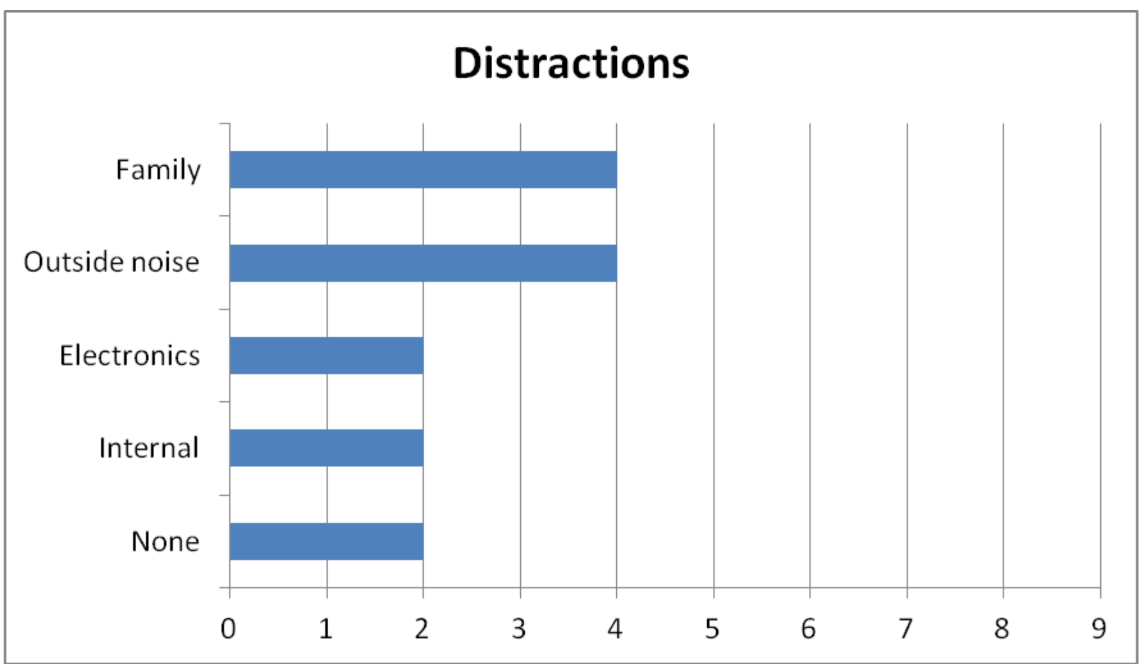


Figure 4 (g). Participant reported burden of training on lives.

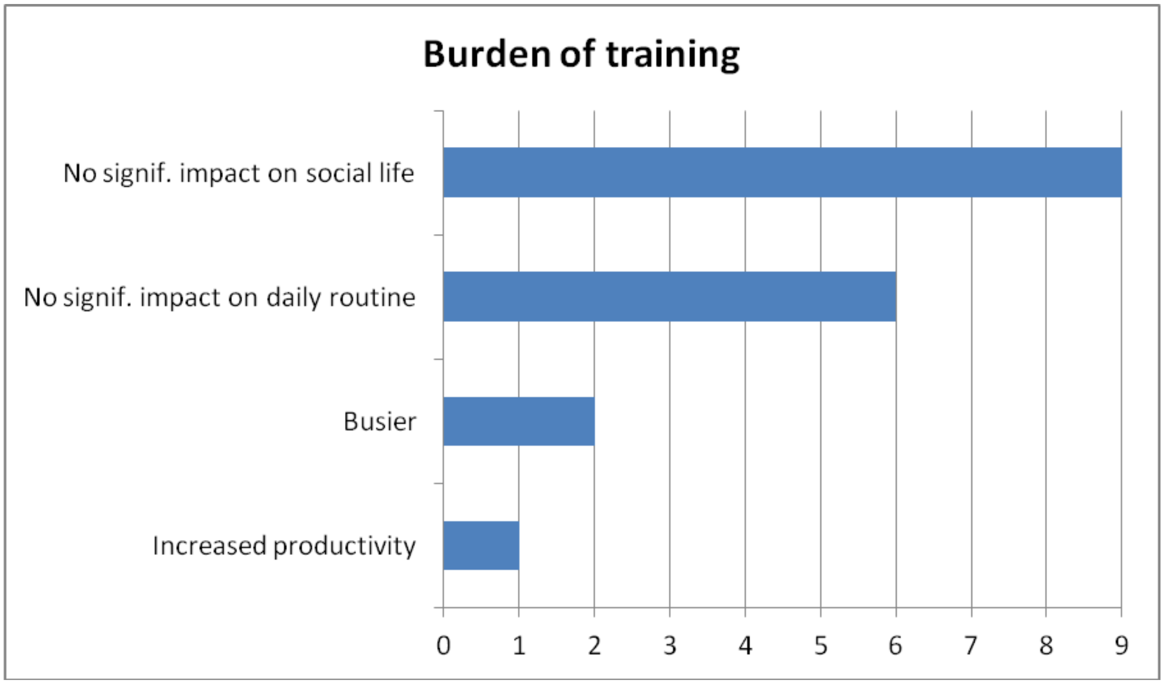
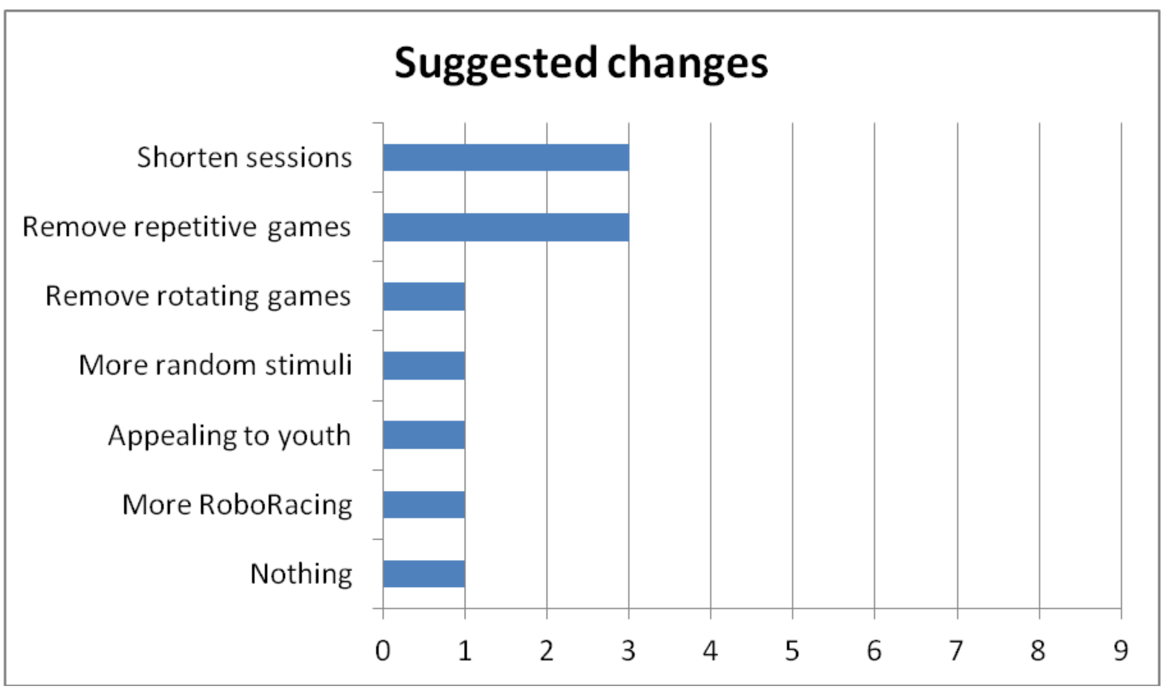


Figure 4 (h). **Participant suggested changes to improve training program.**



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Appendices

Appendix A: Checklist that Training Coach went through before each phone call with participants.

1. Has the user trained all the days he/she is supposed to?
2. Is the effective training time accurate (30-45 minutes excluding pauses)?
3. What level is the Training index at?
4. Is the user training at their optimal level?
5. Are the results even or extremely uneven?
6. Is there a specific order of exercises?
7. What time of the day is the training carried out?
8. How is the user's motivation?
9. Signs of technical difficulties?
10. Recommendations/feedback during next call?

Appendix B: Patient weekly follow-up questionnaire that Training Coach completed during each phone call with participants.

PATIENT WEEKLY FOLLOW-UP QUESTIONNAIRE

Cogmed User ID:	Cogmed Coach:

1. Have any new symptoms arisen related to MS? YES NO

If YES, please describe:

____

____

2. Have there been any significant changes in day-to-day life (e.g., break-up with a partner, death in the family, etc.)?

YES NO

If YES, please describe

____

____

____

3. How would you rate your <u>overall</u> amount of effort used during training?

1	2	3	4	5
No effort	Little effort	Moderate effort	Almost all my effort	All my effort

4. How would you rate your overall level of attention during training?

1	2	3	4	5
Not paying attention	Paying little attention	Paying moderate attention	Almost fully paying attention	Paying full attention

5. How would you rate your overall level of enjoyment during training?

1	2	3	4	5
No enjoyment	Little enjoyment	Moderate enjoyment	Almost fully enjoyed	Fully enjoyed

6. How would you rate your overall motivation to do training?

1	2	3	4	5
No Motivation	Little motivation	Moderate motivation	Almost fully motivated	Fully motivated

Appendix C: Case History Form completed by the patient if he/she was over the age of 16 or by a parent/guardian if he/she was under the age of 16.

CASE HISTORY FORM

This information is confidential and for professional use only.

Date of cognitive testing: Time:

Subject ID number:

Name:

Date of Birth: (mm/dd/yy)

Current age:Sex: F M

Current address:____

Current home phone number:_______________________

Alternative phone number: ______________________________________

Name of current/past school: ______________________________________

Subject ID number:

Current or highest grade level completed:

Mother's age:____ Mother's occupation:

Highest level of school completed by

mother:_____________________________________

Father's age: ____ Father's occupation:

Highest level of school completed by father:

____

Current marital status of parents:

[ ] Married/Common-law [ ] Divorced [ ] Separated [ ] Widowed

City and Country of Birth: _______________________________

Duration living in birth country:

If not from Canada, has your family been in Canada 5 years or more? [ ] yes [ ] no

First language spoken: ______________________________

Most common language spoken at home: [ ] English [ ]

Other:_________________

[ ] Combination of English and other language _________________

Ancestry: □ European □ Asian □ Middle Eastern □ Central/South America

□ African □ Caribbean □ Aboriginal □ Unknown

Subject ID number:

□ Mixed specify):

Race: □ Caucasian □ Oriental □ Black □ Unknown

□ Mixed:___________

MS Specific Questions

Have you received any corticosteroid / IVIg treatment for an attack at least 6 weeks prior to participating in this research study? [ ] Yes [ ] No

Prescribed Medication at time of testing

*used for more than 14 days within 3 months prior to study visit

List	Dose	Ongoing (Y / N)	Duration	Reason for use

Supplements / Vitamins (including allergy, herbal or alternative meds)

*used for more than 14 days within 3 months prior to study visit

List	Dose	Ongoing	Duration	Reason

		(Y / N)		**for use**

Medical History

Were you born full term? (>37 weeks)   [ ] Yes   [ ] No

Have you ever had a head injury? [ ] Yes   [ ] No   If yes, at what age? _________

Did you lose consciousness? [ ] Yes   [ ] No For how long? _______________

Do you wear [ ] Glasses? [ ] Contact lenses?   Date of last vision test: _________

Reason for corrective lenses? (e.g. for distance, for reading):

____

Do you have colour vision loss?   [ ] Yes   [ ] No

Have you ever had or been diagnosed with the following:

Kidney disease[ ] no[ ] yes – explain:________________

Epilepsy/seizures[ ] no[ ] yes – explain:__________________

Febrile convulsion[ ] no[ ] yes – explain:________________

Respiratory disease[ ] no[ ] yes – explain:________________

Heart disease[ ] no[ ] yes – explain:________________

Subject ID number:

Hematological problems[ ] no[ ] yes – explain:________________

Thyroid disease[ ] no[ ] yes – explain:__________________

Digestive problems[ ] no[ ] yes – explain:________________

Diabetes[ ] no[ ] yes – explain:________________

Hypertension[ ] no[ ] yes – explain:________________

Circulatory disease[ ] no[ ] yes – explain:________________

Cancer[ ] no[ ] yes – explain:________________

Other[ ] no[ ] yes – explain:________________

Behavioural and Mental Health History

Have you ever been assessed by a psychologist or psychiatrist? [ ] No[ ] Yes

Reason and date:

Have you repeated a grade? [ ] No[ ] Yes If yes, which grade(s)? ___________

Are you currently placed in a special education program? [ ] No [ ] Yes

Have you been placed in a special education program in the past? [ ] No [ ] Yes

Regular classroom? [ ] Yes [ ] NoModified classroom: [ ] Yes [ ] No

Subject ID number:

Have you ever had or been diagnosed with the following:

Attention Deficit Disorder[ ] no[ ] yes – explain:_________________

Attention Deficit/Hyperactivity Disorder[ ] no[ ] yes – explain:___________________

Anxiety[ ] no[ ] yes – explain:_________________

Autism Spectrum Disorder[ ] no[ ] yes – explain:_________________

Depression[ ] no[ ] yes – explain:_________________

Any psychiatric disorder[ ] no[ ] yes – explain:_________________

Learning Disability (LD)[ ] no[ ] yes – explain:_________________

Language Disorder[ ] no[ ] yes – explain:_________________

Giftedness[ ] no[ ] yes – explain:_________________

Please provide any additional comments you think might be helpful._

Appendix D: Baseline cognitive characteristics of individuals who participated in the study (N = 9).

Study ID	WASI Vocabulary[a]	WASI Matrix Reasoning[a]	RAVLT Trial Total[b]	SDMT Total[c]	Auditory Working Memory	Numbers Reversed	Finger Windows	MSNQ-Patient (raw score)[d,e]	PedsQL – Cognitive fatigue subscale (raw score)[f]
COG_02	0.75	-0.50	1.12	1.69	0.55	1.16	-0.67	26	14
COG_05	1.42	1.13	0.09	0.48	1.08	1.88	0.00	Unavailable	21
COG_06	-1.58	0.33	-0.81	0.85	0.00	-0.50	-1.33	2	8
COG_07	0.75	0.67	-2.10	0.40	1.08	1.25	-0.33	8	3
COG_08	-0.67	-0.33	-0.99	0.50	-0.13	Unavailable	-2.00	19	12
COG_09	1.33	0.67	-1.29	-0.31	0.25	-0.31	0.33	35	12
COG_10	-0.75	-2.25	-0.12	-0.21	-0.62	-1.83	-0.67	20	7
COG_12	0.00	0.41	-0.19	0.15	0.67	0.28	-0.67	23	14
COG_15	-0.13	-0.13	0.10	0.72	-1.25	-1.50	-3.00	20	11

Note. Unless otherwise stated, data are presented as z-scores.

[a]Wechsler Abbreviated Scale of Intelligence (WASI).

[b]Rey Auditory Verbal Learning Test (RAVLT).

[c]Symbol Digits Modalities Test (SDMT).

[d]MS Neuropsychological Screening Questionnaire (MSNQ).

[e]Elevated scores are indicative of high risk for neuropsychological impairment (cut-off score is 23).

[f]Maximum score possible is 24.

Appendix E: Overall and exercise-specific training outcomes of adherent vs. non-adherent individuals presented as mean scores (SD), using Independent-Samples Mann-Whitney U-test for equality of means.

Outcome	**Adherent (N = 6)**	**Non-adherent (N = 3)**[a]
Overall training		
Number of sessions trained*	25.00 (0.00)	16.33 (10.02)
Length of training period (calendar days)	40.67 (6.44)	93.33 (76.54)
Number of Coach phone calls*	5.00 (1.10)	2.33 (1.16)
Mean active time per day (minutes)	45.63 (4.91)	44.82 (8.43)
Mean pause time per day (minutes)	5.57 (2.65)	14.71 (17.63)
Exercise-specific improvement[a]		
Visuo-Spatial Performance Improvement	1.18 (0.33)	0.66 (0.67)
Verbal Performance Improvement	2.49 (1.78)	2.07 (0.29)

*****$p < .05$

[a]For exercise-specific improvement values, data is based on two non-adherent individuals because of insufficient data from the third non-adherent individual who only trained for five days.

Appendix F: Case Summaries.

COG_15

COG_15 is a 17-year-old female who was diagnosed with pediatric-onset MS at the age of 7.6 years. She has had the disease for 10.3 years and has experienced 13 relapses. Her normalized brain volume fell within the Borderline range (z = -1.74) and was the lowest of all nine participants. Her IQ fell within the Average range (IQ = 98), and she indicated a high level of motivation for change at baseline assessment (MCQ score = 26). Her score on a self-report measure of cognitive complaints was below the cut-off, indicating that she is not at high risk for neuropsychological impairment (MSNQ-Patient = 20).

With respect to the computerized training, she was considered compliant and completed 25 sessions over 34 calendar days, with a mean active per day of 43 minutes. Her Verbal WM performance improvement value was 0.43 and was the lowest of all nine participants. Her Visual WM performance improvement value was 1.15. On neuropsychological testing, her WM index change score from baseline to post-training fell within the High Average range (z = 0.96). Her score on a self-report measure of fatigue increased by one point from baseline to post-training.

With respect to her qualitative experiences, she described the training as helpful and she reported changes in two domains. She reported no barriers to training and acknowledged that praise from family was supportive during training.

COG_08

COG_08 is a 24-year-old male who was diagnosed with pediatric-onset MS at the age of 17.1 years. He has had the disease for 7.6 years and has experienced 2 relapses. His normalized brain volume fell within the Low Average range (z = -1.17). His IQ fell within the Average range (IQ = 91), and he indicated a high level of motivation for change at baseline assessment (MCQ score = 27). His score on a self-report measure of cognitive complaints was below the cut-off, indicating that he is not at high risk for neuropsychological impairment (MSNQ-Patient = 19). With respect to the computerized training, he was considered compliant and completed 25 sessions over 41 calendar days, with a mean active per day of 38 minutes. His Verbal WM performance improvement value was 1.38; his Visual WM performance improvement value was 1.33. His WM index change score from baseline to post-training was not available. His score on a self-report measure of fatigue did not change from baseline to post-training.

With respect to his qualitative experiences, he described the training as helpful and that he enjoyed it. He reported changes in one domain. He acknowledged that low motivation served as a barrier to training. He acknowledged that the coaching component was supportive during training and that he used extrinsic rewards.

COG_10

COG_10 is a 14-year-old male who was diagnosed with pediatric-onset MS at the age of 12.6 years. He has had the disease for 2.0 years and has experienced 1 relapse. His normalized brain volume fell within the Low Average range (z = -1.15). His IQ fell within the Borderline range (IQ = 78), and he indicated a high level of motivation for change at baseline assessment (MCQ score = 26). His score on a self-report measure of cognitive complaints was below the cut-off, indicating that he is not at high risk for neuropsychological impairment (MSNQ-Patient = 20).

With respect to the computerized training, he was considered noncompliant and completed 20 sessions over 135 calendar days, with a mean active per day of 54 minutes. His Verbal WM performance improvement value was 1.86; his Visual WM performance improvement value was 0.18 and was the lowest of all nine participants. On neuropsychological testing, his WM index change score from baseline to post-training fell within the Average range (z = 0.33). His score on a self-report measure of fatigue decreased by five points from baseline to post-training.

With respect to his qualitative experiences, he described the training as helpful and that he enjoyed it. He also described the training as time-consuming and boring. He reported changes in two domains. He acknowledged that school served as a barrier to training. He acknowledged that praise from family and extrinsic rewards were supportive during training.

COG_05

COG_05 is a 22-year-old female who was diagnosed with pediatric-onset MS at the age of 16.7 years. She has had the disease for 6.2 years and has experienced 6 relapses. Her normalized brain volume fell within the Average range (z = -0.15). Her IQ fell within the Superior range (IQ = 122), and she indicated a moderate level of motivation for change at baseline assessment (MCQ score = 20). Her score on a self-report measure of cognitive complaints was not available.

With respect to the computerized training, she was considered compliant and completed 25 sessions over 46 calendar days, with a mean active per day of 49 minutes. Her Verbal WM performance improvement value was 2.14; her Visual WM performance improvement value was 1.19. On neuropsychological testing, her WM index change score from baseline to post-training fell within the High Average range (z = 1.01). Her score on a self-report measure of fatigue decreased by 23 points from baseline to post-training.

With respect to her qualitative experiences, she described the training as helpful and that she enjoyed it, though it did feel like a chore. She acknowledged the value of the overall rehabilitation program. She reported changes in four domains. She acknowledged that school and low motivation served as barriers to training. She acknowledged that praise from family/friends and extrinsic rewards were supportive during training.

COG_12

COG_12 is a 16-year-old female who was diagnosed with pediatric-onset MS at the age of 14.2 years. She has had the disease for 1.9 years and has experienced 5 relapses. Her normalized brain volume fell within the Low Average range (z = -0.74). Her IQ fell within the Average range (IQ = 103), and she indicated a high level of motivation for change at baseline assessment (MCQ score = 26). Her score on a self-report measure of cognitive complaints was at the cut-off, indicating that she was close to being at high risk for neuropsychological impairment (MSNQ-Patient = 23).

With respect to the computerized training, she was considered noncompliant and completed 24 sessions over 140 calendar days, with a mean active per day of 39 minutes. Her Verbal WM performance improvement value was 2.27; her Visual WM performance improvement value was 1.14. On neuropsychological testing, her WM index change score from baseline to post-training fell within the High Average range (z = 0.72). Her score on a self-report measure of fatigue decreased by 17 points from baseline to post-training.

With respect to her qualitative experiences, she described the training as helpful, time-consuming, and boring. She reported changes in three domains. She acknowledged that school and low motivation served as barriers to training. She acknowledged that praise from family and extrinsic rewards were supportive during training.

COG_02

COG_02 is a 16-year-old female who was diagnosed with pediatric-onset MS at the age of 15.7 years. She has had the disease for 0.9 years and has experienced 2 relapses. Her normalized brain volume fell within the Average range (z = -0.66). Her IQ fell within the Average range (IQ = 102), and she indicated a moderate level of motivation for change at baseline assessment (MCQ score = 21). Her score on a self-report measure of cognitive complaints was above the cut-off, indicating that she was at high risk for neuropsychological impairment (MSNQ-Patient = 26).

With respect to the computerized training, she was considered compliant and completed 25 sessions over 50 calendar days, with a mean active per day of 44 minutes. Her Verbal WM performance improvement value was 2.58; her Visual WM performance improvement value was 1.58 and was the highest value of all nine participants. On neuropsychological testing, her WM index change score from baseline to post-training fell within the Average range (z = 0.57). Her score on a self-report measure of fatigue decreased by 1 point from baseline to post-training. With respect to her qualitative experiences, she described the training as helpful and that she enjoyed it, though it was time-consuming. She reported changes in three domains. She acknowledged that school served as a barrier to training. She acknowledged that extrinsic rewards and intrinsic motivation were supportive during training.

COG_06

COG_06 is a 14-year-old female who was diagnosed with pediatric-onset MS at the age of 12.0 years. She has had the disease for 2.2 years and has experienced 1 relapse. Her normalized brain volume fell within the Average range (z = -0.53). Her IQ fell within the Low Average range (IQ = 89), and she indicated a high level of motivation for change at baseline assessment

(MCQ score = 27). Her score on a self-report measure of cognitive complaints was below the cut-off, indicating that she was not at high risk for neuropsychological impairment (MSNQ-Patient = 2).

With respect to the computerized training, she was considered compliant and completed 25 sessions over 34 calendar days, with a mean active per day of 52 minutes. Her Verbal WM performance improvement value was 2.72; her Visual WM performance improvement value was 0.58. On neuropsychological testing, her WM index change score from baseline to post-training fell within the Average range (z = 0.21). Her score on a self-report measure of fatigue decreased by 10 points from baseline to post-training.

With respect to her qualitative experiences, she described the training as helpful and repetitive. She reported changes in two domains. She acknowledged that school and extra-curricular activities served as barriers to training. She acknowledged that extrinsic rewards, praise from family, and intrinsic motivation were supportive during training.

COG_09

COG_09 is a 22-year-old male who was diagnosed with pediatric-onset MS at the age of 18.5 years. He has had the disease for 4.2 years; the number of relapses is unknown. His normalized brain volume fell within the Average range (z = 0.19). His IQ fell within the High Average range (IQ = 118), and he indicated a high level of motivation for change at baseline assessment (MCQ score = 27). His score on a self-report measure of cognitive complaints was above the cut-off, indicating that he is at high risk for neuropsychological impairment (MSNQ-Patient = 35).

With respect to the computerized training, he was considered compliant and completed 25 sessions over 39 calendar days, with a mean active per day of 47 minutes. His Verbal WM performance improvement value was 5.69 and was the highest value of all nine participants. His Visual WM performance improvement value was 1.24. His WM index change score from baseline to post-training was within the High Average range (z = 0.85). His score on a self-report measure of fatigue decreased by two points from baseline to post-training.

With respect to his qualitative experiences, he described the training as helpful, time-consuming, repetitive, and feeling like a chore. He acknowledged the value of the overall rehabilitation program. He reported changes in three domains. He acknowledged that low motivation served as a barrier to training. He acknowledged that the coaching component was supportive during training and that he used intrinsic motivation.