Assessment of Attention Network Function in Multiple Sclerosis

by

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Abstract

Cognitive deficits are highly prevalent in multiple sclerosis (MS). Impaired cognitive functions, such as attention abilities, can be among the most limiting changes in individuals rated as having low neurologic disability. Attention is a fundamental cognitive function which plays a role in many tasks conceptualized as assessing other cognitive domains. The Dalhousie Computerized Attention Battery (DalCAB) is a novel computerized assessment, not yet used in MS, that includes 8 tasks. These tasks measure the functioning of three attention networks (executive control, orienting, and vigilance). Slowed response times (RT) and intra-individual variability (IIV) in RT are sensitive indicators of cognitive change in MS and can be calculated for each DalCAB task.

This thesis aimed: To demonstrate validity of the DalCAB tasks as measures of attention network functioning in persons with MS (Aim 1), to examine whether differences in mean-level RT or IIV on the DalCAB tasks are seen in those without clinical evidence of cognitive impairment (Aim 2), to examine whether symptoms of anxiety, depression, pain, and fatigue account for variation in attention network performance and IIV (Aim 3), and to examine whether MRI measures of brain structure and damage are associated with attention network performance or IIV (Aim 4).

Persons with relapsing-remitting MS [Expanded Disability Status Scale (EDSS) ≤ 4.5] were recruited. MS participants (n = 104; M age = 46.0) were mainly female (87.5%) with varying years of education (11-19 years). Median EDSS was 1.9 (interquartile range = 1.5 - 2.5). Control participants matched on age, gender, and years of education were also recruited (n = 40). Participants completed the DalCAB, standard neuropsychological tests, and self-report questionnaires. A sub-set of MS and control participants completed an MRI.

Aim 1: MS participants differed from controls on DalCAB measures reflecting all three attention networks (executive control, orienting, and vigilance) even after accounting for baseline RT differences between groups. Analyses demonstrated initial validity of the DalCAB in this MS sample with regard to known groups validity, ecological validity, and concurrent validity. Aim 2: MS participants unimpaired on standard neuropsychological tests (n = 65) differed from controls in executive control and vigilance network performance, but not orienting. Of the two measures of IIV examined, individual standard deviation (ISD) was better able to distinguish between groups than coefficient of variation. ISD differed between MS participants who were unimpaired on standard neuropsychological tests and controls. Aim 3: Symptoms of anxiety, depression, pain, and fatigue did not explain variability in attention network performance but did explain variability in ISD. Aim 4: MRI measures of brain structure and damage differed between MS and control participants, however, a measure of brain atrophy (i.e., brain parenchymal fraction) did not. MRI measures were not associated with attention network performance. There were limited associations between ISD on some tasks and MRI measures.

The knowledge generated from the thesis has contributed to understanding attention network performance in persons with MS considered to have low neurologic disability.

List of Abbreviations and Symbols Used

ACPC	Anterior Commissure - Posterior Commissure
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ANT	Attention Network Test
ANT-I	Attention Network Test – Interactions
BICAMS	Brief International Cognitive Assessment for Multiple Sclerosis
BPF	Brain Parenchymal Fraction
BRB	Brief Repeatable Battery
BVMT-R	Brief Visuospatial Memory Test – Revised
CI	Cognitive Impairment
CIS	Clinically Isolated Syndrome
CNS	Central Nervous System
CoV	Coefficient of Variation
COWAT	Controlled Oral Word Association Test
CRT	Choice Reaction Time Task
CSF	Cerebral Spinal Fluid
CTIP	Computerized Test of Information Processing
CVLT-II	California Verbal Learning Test – Second Edition
DalCAB	Dalhousie Computerized Attention Battery
DICOM	Digital Imaging and Communications in Medicine
DSM	Diagnostic and Statistical Manual of Mental Disorders
DT	Dual Task

Dx	Diagnosis
EDSS	Expanded Disability Status Scale
ERP	Event Related Potential
FSPGR	Fast Spoiled Gradient Recalled Echo
FIS	Fatigue Impact Scale
FLAIR	Fluid-Attenuated Inversion Recovery
FOV	Field of View
GNG	Go-No-Go Task
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale, anxiety subscale
HADS-D	Hospital Anxiety and Depression Scale, depression subscale
HRQoL	Health-related Quality of Life
HUI	Health Utility Index
IIV	Intra-Individual Variability
IM	Item Memory Task
ISD	Individual Standard Deviation
LNS	Letter-Number Sequencing
LST	Lesion Segmentation Toolbox
M	Mean
MACFIMS	Minimal Assessment of Cognitive Function in MS
MANOVA	Multivariate Analysis of Variance
mm^3	Cubic millimeter
MNI	Montreal Neurologic Institute

MOS-PES	Medical Outcomes Study – Pain Effects Scale
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
n	Sample size
η^2_p	Partial eta squared
NIFTI	Neuroimaging Informatics Technology Initiative
NINDS	National Institute of Neurological Disorders and Stroke
PASAT	Paced Auditory Serial Addition Test
PDDS	Patient Determined Disease Steps
PPMS	Primary Progressive Multiple Sclerosis
r_s	Spearman correlation coefficient
RIS	Radiologically Isolated Syndrome
RRMS	Relapsing-Remitting Multiple Sclerosis
RT	Reaction Time
SD	Standard Deviation
SDMT	Symbol Digit Modalities Test
SPMS	Secondary Progressive Multiple Sclerosis
SRT	Simple Reaction Time Task
t	T-score
TE	Echo time
TI	Inversion time
TR	Repetition time
USA	United States of America

VF	Vertical Flanker Task
VS	Visual Search Task
WTAR	Wechsler Test of Adult Reading
X^2	Chi-squared
z	Z-score

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Chapter 1. General Introduction

Multiple sclerosis (MS) is an autoimmune disease characterized by demyelination of the central nervous system (CNS) and neurodegeneration. Clinical symptoms of the disease vary widely depending on the area of the CNS affected. Common examples include: loss of vision and sensation, tremor, poor balance, impaired swallowing, muscle stiffness and spasms, and cognitive deficits (Compston & Coles, 2008). Initial presentation of the disorder often includes inflammation of the optic nerve or spinal cord leading to temporary loss of vision, pain, or muscle weakness (i.e., optic neuritis or transverse myelitis; Chung et al., 2019; Koch, Uyttenboogaart, van Harten, & De Keyser, 2008). Loss of motor functions are common over time, with 50% of individuals requiring assistance with walking after less than 15 years of living with MS (Weinshenker et al., 1989). The exact cause of MS is currently unknown, although genetic, lifestyle, and environmental factors contribute to the risk of developing the disorder such as vitamin D deficiency, smoking, and obesity (Hedström et al., 2017; Hedström, Olsson, Kockum, Hillert, & Alfredsson, 2020; Huppke et al., 2019). Approximately three females are affected to every male (Kingwell et al., 2015; Marrie et al., 2013; Wallin et al., 2019). Although pediatric MS does occur, MS is commonly diagnosed between the ages of 20 and 45, an individual's productive adult years (Liguori et al., 2000; Waldman et al., 2016). As these are the years in which individuals may obtain advanced education, establish their career, or bear children, the economic and personal impact of MS is substantial. The majority of people with MS report giving up their employment or retiring early due to the disease, and many report a

decline in their standard of living due to employment changes and/or costs associated with the disorder (Hakim et al., 2000). In a survey of 916 people with MS in the United Kingdom, 76% were receiving government benefits (G. Green, Todd, & Pevalin, 2007). Canadian older adults with MS (i.e., 55+ years of age) were found to be eight times less likely to be employed compared to other Canadians in their age group (Ploughman et al., 2014). Social activities, intimate relationships, and health-related quality of life are just a few of the other areas affected in persons with MS (G. Green & Todd, 2008; Aurélie Ruet, Mathilde Deloire, Delphine Hamel, et al., 2013). In a disorder where the majority of individuals live for 30 years or more after diagnosis (Brønnum-Hansen, Koch-Henriksen, & Stenager, 2004), continued research focusing on factors that impact life with MS is needed.

Western countries in the northern hemisphere generally report the world's highest prevalence of MS, for a number of reasons. Latitude gradients have been identified, where by locations further away from the equator record higher prevalence (Simpson, Blizzard, Otahal, Van der Mei, & Taylor, 2011). Environmental factors such as low sun exposure, mediated by vitamin D intake, have been shown to contribute to this latitude gradient; Hedström and colleagues (2020) looked at vitamin D levels and self-reported amounts of sun exposure, concluding that these were both independent contributors and interact with each other to increase MS risk. For example, Kampman and Brustad (2008) reviewed relevant MS research in Norway and found that despite low sun exposure, persons in Norway have reduced their MS risk by eliminating vitamin D deficiency through

supplementation and traditional fish diets. Early work suggests that individuals moving from a low-risk country to a higher risk country maintained the low-risk associated with their country of origin depending on how early in life the move took place, suggesting a critical period for environmental factors (Gale & Martyn, 1995). Exceptions to the latitude gradient are reported, as described above regarding Norway and elsewhere such as Italy, yet variability in how prevalence is evaluated between latitude-gradient studies can make comparisons difficult (Evans et al., 2013; Kingwell et al., 2013).

Differences among ethnic groups also contribute to higher MS prevalence in western countries. Smedstad, Sandvik, Holmoy, Harbo, and Celius (2008) recruited persons with MS living in Norway, based on their country of origin. They found the prevalence of MS to be higher in individuals of Norwegian/Western origin versus Asian, African, or Middle Eastern. Similarly, the prevalence of MS was higher in non-Hispanic white individuals in Texas, United States of America (USA), compared to Hispanic and non-Hispanic Black individuals (Williamson, Henry, Schiffer, & Wagner, 2007). In Canada, prevalence of MS ranges from coast to coast: Nova Scotia reports 266.9/100,000 individuals have MS, Manitoba 262.4/100,000, and British Colombia 179.9/100,000 (Kingwell et al., 2015; Marrie et al., 2013; Marrie, Yu, Blanchard, Leung, & Elliott, 2011). All three of these studies used administrative provincial health data and similar case definitions to provide their prevalence estimates. A recent estimate of the prevalence of MS in the USA reported the highest numbers to date at 309.2/100,000, representing 727,344 individuals with the disorder (Wallin et al., 2019). Although it is difficult to

compare between studies of varying methodologies, these patterns indicate that continued research on MS is of particular importance to those living in North America.

1.1 Diagnosing MS

The first clinical case, of what would later be named MS, was described by neurologist Jean-Martin Charcot in his 1868 lecture series. Although he acknowledged the contributions of his fellow neurologist, Alfred Vulpian, and of those before him who had studied the pathology of the disease, it was Charcot who provided the first comprehensive report encompassing both anatomy and symptomatology (Charcot, 1877).

There is no single clinical feature or diagnostic test that identifies MS. Diagnostic criteria have seen several iterations over the years and currently rely on clinical, imaging, and laboratory findings (Thompson et al., 2018). The “Poser Criteria” were the first to incorporate evidence from evaluations beyond a clinical exam, such as evoked potential studies (Poser et al., 1983). Although the next major update was not until the internationally recognized “McDonald criteria” (McDonald et al., 2001), further revisions have been published in relatively rapid succession to accommodate quickly evolving neuroimaging methods, laboratory technologies, and research. These include: 2005 Revisions (Polman et al., 2005), 2010 Revisions (Polman et al., 2011), and the 2017 Revisions (Thompson et al., 2018).

A combination of evidence demonstrating (1) clinical relapses and (2) CNS lesions has long been central in the diagnostic criteria of MS. The term “relapse”

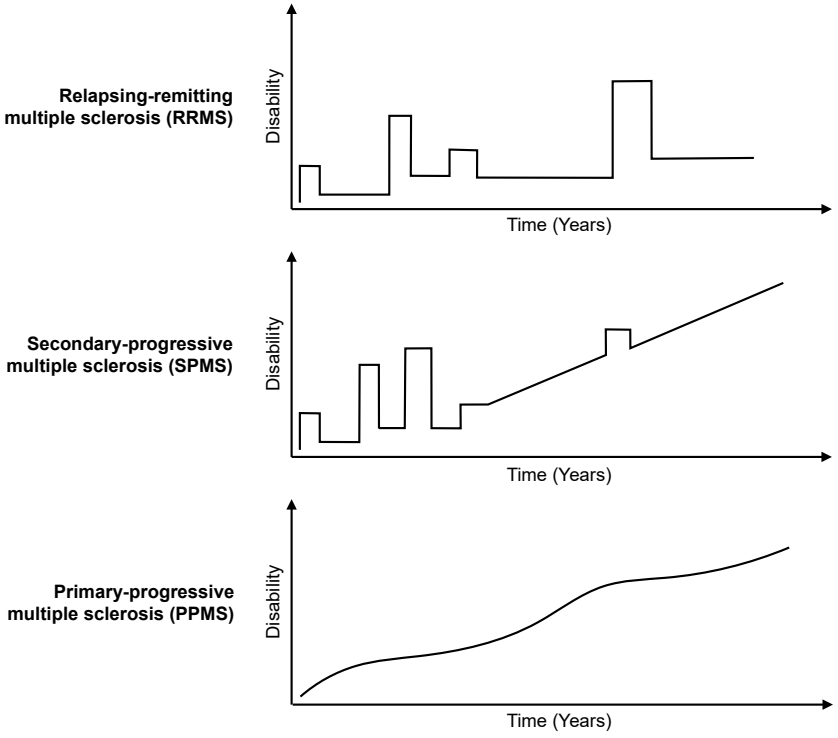
or “attack” is used to describe demyelinating events in the CNS and the associated clinical symptoms (Thompson et al., 2018). The exact process of the demyelinating events is still under debate, however, inflammation, neuroglial depletion, and axon degeneration is all known to occur (Compston & Coles, 2008). Since the significant integration of magnetic resonance imaging (MRI) findings into the 2001 McDonald criteria, demonstrating “dissemination of lesions in both space and time” on neuroimaging has become a standard diagnostic necessity (i.e., lesions in more than one area of the CNS on more than one occasion; McDonald et al., 2001). The newest 2017 criteria require a combination of clinical relapses and lesions, however, now additionally allow cerebral spinal fluid (CSF)-specific oligoclonal bands to be used in place of demonstrating demyelination over time, so to allow for earlier diagnoses of MS (Thompson et al., 2018). CSF-specific oligoclonal bands indicate antibody production, representative of an inflammatory response. The time from onset of MS to diagnosis has decreased by upward of 5 years for those born in the 1900’s (Celius & Smestad, 2009). Earlier and more accurate diagnoses of MS has opened the door to new research examining individuals in the milder stages of disease.

1.2 Subtypes of MS

Three main subtypes of MS are recognized by the International Advisory Committee on Clinical Trials of MS: Relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS; Lublin et al., 2014; See Figure 1). RRMS is the most common subtype, representing approximately 80-90% of cases (Tremlett, Zhao, Rieckmann, & Hutchinson, 2010). In RRMS,

individuals experience clinical relapses (i.e., “episodic acute period of worsening”) followed by a period of remission (p. 907, Lublin & Reingold, 1996). Individuals do not necessarily return entirely to baseline function between relapses. Over time, the disease may change to a course of continually accumulating deficits, with or without relapses. Individuals who enter this progressive disease course after having initially meet criteria for RRMS would then be classified as SPMS. The median time to progress from RRMS to SPMS is approximately 15-20 years (derived from graph; Tremlett et al., 2010), yet no clear criteria exists to identify exactly when the transition from RRMS to SPMS occurs (Lublin et al., 2014). The remaining MS cases, whose disease course is one of insidious decline from onset, are classified as having PPMS (Lublin & Reingold, 1996). PPMS is considered to be part of the same disease spectrum as RRMS and SPMS, however, the differences in pathology between RRMS/SPMS and PPMS are not well understood (Antel, Antel, Caramanos, Arnold, & Kuhlmann, 2012). For example, 18 disease modifying drugs are approved for use in RRMS and/or SPMS, whereas only one has successfully received approval for use in PPMS (National MS Society, 2019, Nov).

Figure 1. Subtypes of MS.



Additional labels are common in the MS literature, however, are not subtypes of the disorder. The term “clinically isolated syndrome” (CIS) is used for individuals who have not received a diagnosis MS, yet have experienced a single clinical attack likely indicative of MS without meeting the full criteria (i.e., have not shown dissemination in time; Thompson et al., 2018). In a sample of 122 persons with CIS, 65.6% had converted to MS at 30 years post-CIS diagnosis (Chung et al., 2019). Individuals who presented with symptoms relating to the brainstem (e.g., vertigo, impaired speech, and swallowing) were more likely to convert to MS compared to those who presented with optic neuritis or transverse myelitis. “Radiologically isolated syndrome” (RIS) is used to describe individuals who show strong evidence of MS neuropathology on MRI, however, have not had a clinical attack or symptoms (Thompson et al., 2018). Even before the onset of symptoms

relating to demyelinating disease (e.g., CIS and RIS), emerging research suggests there is a prodromal period of symptoms. A retrospective examination of individual health claims data found that persons who developed MS were significantly more likely to have physician or hospital encounters compared to matched control individuals during the five years prior to their first demyelinating event (Wijnands et al., 2019). The term “benign MS” has been used in the literature to refer to individuals with a relatively slow accumulation of neurologic disability over time (Lublin et al., 2014). Although definitions vary, benign MS is often used to describe those who have limited neurologic disability (i.e., a score of 3 or less on the Expanded Disability Status Scale) despite a disease duration of 10 years or more (Reynders, D'haeseleer, De Keyser, Nagels, & D'hooghe, 2017). Pediatric onset of MS, with a mean onset between 12 to 16 years of age, accounts for 2.2% to 9.5% of MS cases across cohort studies. Among pediatric onset cases, approximately 98% have the RRMS subtype (Waldman et al., 2016).

1.3 Disease Course and Treatment

Predicting prognosis and disease course has been a longstanding issue in MS research, even within individuals of the same subtype (Eriksson, Andersen, & Runmarker, 2003; Runmarker & Andersen, 1993). A review of research relating to the natural history of MS described it as a “notoriously variable” disease and highlighted the discrepancies in positive prognostic characteristics identified between studies (p. 2005, Tremlett et al., 2010). Additional methods that can assist with monitoring or predicting disease progression are becoming increasingly necessary as new disease modifying drugs continue to be developed. Although no

drug has successfully halted MS, the development of drugs that slow disease progression has advanced substantially (Muraro & Bielekova, 2007). Beginning treatment early after disease onset can result in significant benefits such as decreased relapse rate and disability accumulation (Coles et al., 2005). As persons with MS are taking longer to progress to more significant disability and/or are experiencing fewer relapses (Costello & Kalb, 2019), increasingly more individuals are spending additional time in milder stages of disease. However, disease modifying drugs vary in their aggressiveness and side effects, with oral, injectable, or intravenous infusion medications available (National MS Society, 2019, Nov). Common side effects among oral treatments include headaches and abnormal liver tests, whereas for more aggressive infusion treatments common side effects include rashes, chest pain, and increased risk of infections. Disease modifying drugs for MS are divided into first, second, and third-line treatments based on the drug's risk-benefit profiles, although knowing when to switch someone to the next line of treatments can be difficult (Dörr & Paul, 2015). Identifying who will and who will not respond to a drug to begin with has also been challenging. For example, Río and colleagues (2006) found that many individual characteristics, such as age, sex, and disease duration, did not differ between treatment responders and non-responders of the drug interferon-beta. Possible indicators of drug response such as neutralizing antibodies (Buck & Hemmer, 2014) are being used clinically to assist in making effective decisions around treatment, however, no one tool has been shown to be sufficient.

Describing disease severity, or neurologic impairment due to MS, has long relied on standardized ratings as established via a neurologic examination. First published by Dr. John Kurtzke in 1955 as the Disability Status Scale (Kurtzke, 1955), and later revised as the Expanded Disability Status Scale (EDSS; Kurtzke, 1983), the EDSS is the most common method of rating MS disease severity. The EDSS divides neurological deficits into eight Functional Systems: pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, and other. For each of these Functional Systems, the examiner must rate the individual's level of disability on a scale from zero to five, or zero to six, depending on the system ("other" is rated only as present or absent). The individual's EDSS score is then graded from zero (i.e., "normal neurologic exam") to 10 (i.e., "death due to MS"), in 0.5 increments. EDSS scores from 0.0 to 2.5 consider solely the number and degree of impaired Functional Systems, but higher ratings rely heavily on the individual's ambulatory abilities (e.g., EDSS of 6.5: "Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting; […] more than two Functional System [with ratings of] 3+"; US Department of Veteran's Affairs, 2018). The EDSS has been criticized for its limitations. For example, the EDSS has been shown to account for limited variance in objective cognitive testing performance (10-15%; Fischer et al., 1994), despite cognitive deficits being a highly prevalent neurologic impairment in MS (Chiaravalloti & DeLuca, 2008). Cognitive dysfunction, as well as common symptoms in MS such as changes in mood and increased fatigue, are only captured in the "other" category of the EDSS Functional Systems, which are rated as "present" or "absent" instead of an ordinal

scale. A recent systematic literature review of the EDSS stated that it “has been used preferentially as primary and secondary outcome measurement” in clinical trials thus far (p. 6, Meyer-Moock, Feng, Maeurer, Dippel, & Kohlmann, 2014). As EDSS is the primary tool for assessing neurologic disability in MS, this means that individuals considered to have low neurologic disability may actually have significant cognitive impairments that interfere with their ability to function independently. This discrepancy raises concerns for treatment trials in MS, which may be undervaluing the cognitive benefits of new drugs (Lloyd, Schofield, & Adlard, 2020).

1.4 Neuropathology of MS

MS is characterized by diffuse demyelination of the white matter in the CNS, resulting in axonal degeneration and neuronal death (Compston & Coles, 2008). These demyelinating events lead to the classic white matter plaques typically observed in MS. Focal demyelinated lesions in the white matter are thought to be caused by a variety of inflammatory processes, whereby the body’s immune cells attack the myelin. As mentioned above, the exact process of these demyelinating events is still under debate, consistent with the limited effectiveness of MS treatments targeting the immune response (Lassmann, Brück, & Lucchinetti, 2007). In RRMS, extensive remyelination of the white matter occurs resulting in either complete or partial functional recovery following an acute relapse, leading to the “relapsing-remitting” nature of this MS subtype. Yet remyelination is thought to occur less frequently as the disease progresses, and in progressive forms of the disease (i.e., SPMS and PPMS). Normal-appearing white matter on conventional

MRI, that does not contain visible lesions, has been shown post-mortem to contain changes in pathology such as axonal swelling and increased numbers of enlarged microglia/macrophages (Moll et al., 2011). Moll and colleagues (2011) used non-conventional MRI techniques, such as magnetic transfer ratio and diffusion tensor imaging, to identify some changes in white matter that did not appear on conventional MRI.

Neuronal damage occurring in normal-appearing white matter on MRI is support for the “outside-in” hypothesis of MS, the most common framework for conceptualizing the disease. This framework posits that the pathology of MS begins with immune dysregulation: inflammatory cells attack and destroy the myelin which then leads to axonal degeneration (Stys, Zamponi, Van Minnen, & Geurts, 2012). In the outside-in hypothesis, MS is an autoimmune inflammatory disease. However, there is an alternative “inside-out” hypothesis of MS. This inside-out hypothesis states that degeneration of oligodendrocytes occurs independent of an immune response, and it is in fact this degeneration and subsequently released antigens that trigger an immune response. In this scenario, it is not that inflammation and demyelination are the root cause of neuronal damage due to MS, instead, neurodegeneration is the primary cause. In the inside-out hypothesis, MS is primarily a neurodegenerative disease. Both methods of action may hold true for different subtypes of the disease, with inflammation more prominent in RRMS and neurodegeneration more prominent in SPMS and PPMS. In addition, the inflammatory response may lead to further neurodegeneration and vice versa, creating a “vicious cycle” (p. 510; Stys et al., 2012). This may explain

why immune modulating drugs for MS have some effect, reducing the rate of relapses, but do not halt the disease: the cycle is disrupted.

Lesions and atrophy were previously thought to occur primarily in white matter of the CNS, however, improved histological and imaging methods have demonstrated that grey matter is also affected. In their influential paper, Kutzelnigg and colleagues (2005) performed post-mortem pathological analyses on the whole brain of persons with RRMS, SPMS, PPMS, and controls without MS. Although white matter lesion load was similar across subtypes, persons with RRMS had significantly more active white matter lesions than SPMS/PPMS, whereas SPMS/PPMS had more grey matter demyelination and diffuse white matter inflammation. This was consistent with early work indicating whole brain atrophy occurs in MS and can be detected with conventional MRI (Rudick et al., 1999). Subcortical grey matter structures have since been more thoroughly examined, showing connections to neurologic disability progression (as measured by EDSS). In a study by Eshaghi and colleagues (2018), subcortical grey matter structure volume was the only volume measure at baseline that predicted the time to EDSS progression (i.e., increase of 1.5) approximately two years later, with thalamic volume having the greatest predictive value among the subcortical structures.

1.5 Cognition in MS

Although changes in cognition in MS were described by Charcot in 1868, in the 100 years following his pioneering lecture cognitive dysfunction in MS was generally regarded as uncommon (McKhann, 1982). Epidemiological work on the natural history of MS during that time reported that only 2.9% of individuals

experienced changes in “mentation”, which included both cognitive deficits and changes in affect (Kurtzke et al., 1972). Initial studies examining cognition reported cognitive impairments to be associated with disability severity in MS, suggesting that cognitive deficits were a symptom only for those already experiencing advanced neurological disability due to MS (Canter, 1951; Fink & Houser, 1966; Harrower & Kraus, 1951; Parsons, Stewart, & Arenberg, 1957; Surridge, 1969). However, the methodological approaches used amongst these early studies did not have the benefit of the tools and guidelines used to study cognition in MS today. For example, Kurtzke and colleagues (1972) assessed cognition only as part of a brief mental-status examination with a neurologist, not formal cognitive testing, and Surridge (1969) based their conclusions largely on a patient interview. Fink and Houser (1966) chose to focus on only one area of cognition, verbal abilities (using the Wechsler Adult Intelligence Scale), and concluded that cognition was not changed. Verbal abilities are now known to be relatively unaffected in MS (Grzegorski & Losy, 2017). The methodological approaches hindering the interpretation of research on cognition in MS was critically reviewed by Rao (1986). At that time, he highlighted problems in the diagnosis of MS, variability in disease symptoms, and the effects of mood symptoms on test performance as some of the key issues affecting research on cognition in MS. Dr. Rao went onto be the first to establish the prevalence of cognitive impairments in a community sample of MS, in 1991. His sound methodological approach produced results that have not been contradicted by recent work (Rao, Leo, Bernardin, & Unverzagt, 1991). Since then, research has continued to progress in each of the problematic areas highlighted

by Dr. Rao. For example, as discussed previously, new diagnostic criteria have allowed for MS diagnoses to be more accurate and occur earlier. This is beneficial to studying cognition early in MS disease course, when cognitive dysfunction may be the greatest source of functional impairment and when assessments of cognitive abilities are less influenced by accumulated disability in sensory and motor functions.

In the past 30 years, cognitive dysfunction has developed into a widely recognized and studied issue in MS. Cognitive deficits are now recognized as a common feature of the disorder with estimates by some authors ranging from 43 to 70% of individuals affected, depending on the sample included and how cognition was assessed (Chiaravalloti & DeLuca, 2008). A relatively consistent profile of cognitive deficits has been identified across studies with slowed information processing speed being the primary feature and the domains of working memory, verbal and visual learning/memory, complex attention, and executive functions among the most commonly affected areas (Benedict et al., 2016; Nocentini et al., 2006; Ruano et al., 2017). However, significant variability exists in the reported prevalence of impairments and the exact cognitive processes implicated within each of those cognitive domains. In a recent review of cognitive impairments in MS, Grzegorski and Losy (2017) reported the prevalence of deficits in each cognitive domain, the majority of which had large ranges: information processing speed (20-50%), memory (33-65%), attention (12-25%), executive functions (17-19%), visual perceptual functions (up to 25%). Several factors contribute to this variability.

One factor easily accounted for is the difference between subtypes of MS. Early studies on cognition grouped individuals of different subtypes in the same cohort (Amato et al., 1995), however, a meta-analysis by Zakzanis (2000) that included 1,854 persons with MS and 1,265 healthy controls noted differences between RRMS and progressive forms of MS on tests of verbal skills, attention, executive functioning, and memory. More recent studies have continued to show the prevalence and pattern of cognitive deficits to vary between these groups. Ruano and colleagues (2017) administered a battery of neuropsychological tests to a sample of 873 persons with MS, and found that fewer persons with RRMS met the cut-off for cognitive impairment (44.5%) than those with SPMS (79.4%) and PPMS (91.3%; cut-off = < 5^{th} percentile in two cognitive domains). The pattern of cognitive deficits also appears to differ between subtypes, with RRMS and SPMS exhibiting a similar pattern, yet persons with PPMS having greater executive functioning difficulties (Ruano et al., 2017; Ruet, Deloire, Charré-Morin, Hamel, & Brochet, 2013). In addition, persons with PPMS have been shown to experience three times more cognitive decline annually compared to RRMS, when looking at a mean z-score across a number of cognitive domains over a five year period (Eijlers et al., 2019). Despite clear evidence that patterns of cognitive impairments differ between MS subtypes, some studies on cognition in MS continue to be published with mixed subtype samples.

Other factors that contribute to variability in research on cognition in MS are more difficult to address. Neuropsychological tests are often described as measuring one cognitive function, whereas most tests draw on multiple cognitive

domains and/or may be adversely influenced by an impairment in a cognitive domain other than that typically considered to be measured by that test. For example, the Brief Visuospatial Memory Test (BVMT-R; Benedict, 1997) requires individuals to view an array of figures for 10 seconds and then draw the array from memory, repeated for three trials. The BVMT is often conceptualized as a test of visual memory, however, the task also requires visual-spatial abilities and manual dexterity. Slowed drawing of the figures, which may occur if manual dexterity is affected, results in an additional time for the encoded information to decay from memory. Also, performance may be adversely affected by slowed processing speed given that examinees only have 10 seconds to view the array of figures. In addition, different tasks are used between studies to measure the same cognitive domain, further compounding this issue. For example, within collections of tests compiled to assess cognitive function in MS, “memory” is assessed using the Selective Reminding Test in some batteries and the California Verbal Learning Test in others (Benedict et al., 2016).

Cognitive impairments are often identified in persons only recently diagnosed with MS and those with low levels of neurologic disability due to MS. Although even within this subgroup, and studies only examining persons with RRMS, variability still exists in the reported prevalence of impairment and in the cognitive domains affected (See Table 1). This variability may be due, in part, to the issues with standardized neuropsychological tests described above as well as which cognitive domains were selected to be evaluated. In addition, as can be observed in Table 1, there is variation in how RRMS samples “early in disease

course" were selected. Some authors selected their sample based on time since MS diagnosis and others used a cut-off for accumulation of neurologic disability (i.e., low EDSS scores), given that neurologic disability accrues at different rates between individuals. Lastly, there is some variation in the criteria for "cognitive impairment" between studies. Most commonly, an individual must perform 1.5 to two standard deviations below the "mean", however, the "mean" can be selected based on a control group or published normative values. In addition, the number of tests on which an individual need to perform poorly before they are classified as having "cognitive impairments" also differs, ranging from one to three tests in the studies described in Table 1. The variability in criteria for cognitive impairment across studies would likely have little impact on the variability in research on cognition in MS if the range of neuropsychological tests administered and cognitive domains examined was consistent.

Table 1. Cognitive Impairment (CI) Early in RRMS Disease Course.

Publication Authors (Year)	**RRMS Population**	**Sample Size (*n*)**	**Criteria for CI**	**Prevalence of CI**	**Cognitive Domains Affected***
Deloire and colleagues (2005)	Time since dx: 6 months	MS: 58	-2SD below controls on 2+ tests	45%	Verbal and visual memory, information processing speed, inhibition, verbal abstract reasoning[3]

Publication Authors (Year)	RRMS Population	Sample Size (*n*)	Criteria for CI	Prevalence of CI	Cognitive Domains Affected*
Deloire, Ruet, Hamel, Bonnet, and Brochet (2010)	Time since dx: 6 months	MS: 46 Control: 56	-2SD below controls on 2+ tests	47.8%	Verbal and visual memory, attention, inhibition, verbal abstract reasoning
Amato and colleagues (2004)	Time since onset ≤ 10 years EDSS ≤ 4.0	MS: 41 Control: 16	-2SD below controls on 1+ tests	56.1%	Visual and verbal memory, information processing speed
Amato and colleagues (2010)	Time since onset < 3 years EDSS ≤ 3.5	MS: 49 Control: 56	-1.5SD below controls on 2+ tests	30.6%	Verbal memory[3]
Zivadinov and colleagues (2001)	Time since dx: 1-5 years EDSS ≤ 5.0	MS: 53	Previously published Italian cut-off scores[1]	26.4%[2]	Not reported
Ruggieri and colleagues (2003)	EDSS ≤ 3.5	MS: 50 Control: 50	Compared to controls	Not reported	Verbal and visual memory, visual abstract reasoning, problem solving, facial recognition

Publication Authors (Year)	RRMS Population	Sample Size (*n*)	Criteria for CI	Prevalence of CI	Cognitive Domains Affected*
Correale, Peirano, and Romano (2012)	EDSS < 3, 10 years after onset: "benign MS"	MS: 43 Control: 35	-2SD below controls on 3+ tests	47%	Visual memory, working memory, attention, novel problem solving, visual discrimination
DiGiuseppe, Blair, and Morrow (2018)	Time since dx $\leq$ 1 year	MS: 107	$z = \leq$ -1.5 on each test	Not reported	Verbal and visual memory, information processing speed, attention, novel problem solving, verbal fluency

Note. SD = Standard deviation; Dx = Diagnosis; *Reported cognitive domains classified as impaired at baseline, if a longitudinal study; [1]Spinnler H, Tognoni G. *Standardizzazione e taratura italiana di test neuropsicologici*. Milan: Masson, 1987; [2]Excluded individuals with a low Intelligence Quotient and Mini-Mental State Examination scores; [3]Differed from controls.

In his seminal paper examining the presence of cognitive impairments in a community sample of persons with MS, Dr. Stephen Rao also proposed the first collection of cognitive tests (i.e., "battery" of cognitive tests) to be used in MS specifically: The Brief Repeatable Battery (BRB; Rao, Leo, Bernardin, et al., 1991). The authors administered many cognitive tasks, and selected those which uniquely contributed to identifying cognitive impairments in MS. More recently the International Multiple Sclerosis Cognition Society, in their summary of cognitive

issues in MS, highlighted four additional batteries that have since been developed and validated (Benedict et al., 2016). Listed in chronological order, the four batteries are: (1) Minimal Assessment of Cognitive Function in MS (MACFIMS), (2) National Institute of Neurological Disorders and Stroke (NINDS) Common Data Elements, (3) the Brief Cognitive Assessment of Multiple Sclerosis (BICAMS), and (4) MS-COG. Each of these additional developments has sought to fulfill a need in the MS literature. Following the BRB, which focused on screening for cognitive impairments in MS, the MACFIMS (Benedict et al., 2002) aimed to establish the minimum test battery for clinical neuropsychological assessment when evaluating cognitive function in MS. The MACFIMS requires 90 minutes to administer and additional neuropsychological training which has presented barriers to its use in MS clinics broadly. The subsequent NINDS Common Data Elements (National Institute of Neurological Disorders and Stroke, 2011) differed from the MACFIMS only by removing one test, as the test did not continue to show the same utility and psychometric prosperities as the other included tests. MS-COG (Erlanger et al., 2014) was developed to be used as a composite cognitive endpoint in MS drug trials, using only four of six tests included in the NINDS Common Data Elements. Meanwhile, the BICAMS (Langdon et al., 2012) selected only three previously recommended tests, creating a battery requiring 15 minutes to administer, to be used as a brief cognitive assessment that could be easily implemented in MS clinical settings. These well-defined and validated cognitive testing batteries have all created a foundation on which the extent and impact of cognitive impairments in MS can and have been studied.

Cognitive impairments are associated with a number of the negative outcomes in MS. Persons with MS who are cognitively impaired have been found to be significantly less likely to be working and less independent in their activities of daily living (e.g., meal preparation) despite not differing on measures of physical disability (Rao, Leo, Ellington, et al., 1991). Benedict and colleagues (2005) found that cognitive function accounted for the majority of variability in vocational status in 120 persons with MS, greater than that accounted for by EDSS, disease duration, and symptoms of fatigue. Performance on neuropsychological tests of processing speed, visual perception, and perseverations with problem solving were the individual contributors. Longitudinal work examining predictors of loss of employment over three years similarly found processing speed to play a major role (Morrow et al., 2010). Notably, the authors found that a four-point drop on the Symbol Digit Modalities Test (a test associated with information processing speed) between the first and second testing sessions spaced three years apart, indicated that an individual was 4.2 times more likely to switch from being employed to being unemployed and on paid disability at the second testing session. Similarly, a two-point drop between testing sessions on a test associated with verbal learning and memory (California Verbal Learning Test – Total Recall) indicated an individual was 3.7 times more likely to switch from being employed to being on paid disability. Other research has shown cognitive deficits in MS to be associated with a decrease in self-reported social integration in the community (Hughes et al., 2015), worse self-reported health-related quality of life (Shawaryn, Schiaffino, LaRocca, & Johnston, 2002), and increased self-reported frequency of recent falls even after

controlling for levels of neurologic disability (D'Orio et al., 2012; study used the Incapacity Status Scale, not EDSS).

Initial work examining possible management and treatment strategies for cognitive impairments in MS, such as cognitive rehabilitation and physical exercise training, is limited and recommendations for clinical practice are not yet established (Grzegorski & Losy, 2017). There are some pharmacological treatments for MS that have shown promise with regard to enhancing cognitive functioning, yet none have been found to have a high level of effectiveness and the majority have no effect (See for review: E. Miller, Morel, Redlicka, Miller, & Saluk, 2018). However, variability in the assessment of cognition in MS, mentioned above, creates barriers in developing and evaluating treatments. Sumowski and colleagues (2018) highlighted in their “key priorities” for understanding cognitive deficits in MS that more precise cognitive phenotyping in MS would be necessary for identifying the neural basis of cognitive deficits. The authors additionally highlighted that composite variables would provide more accurate measures of cognitive domains, instead of relying on one task that is typically considered to assess one function.

For persons receiving an initial diagnosis of MS, cognitive deficits may be among the most limiting changes. For example, a study by Deloire and colleagues (2010) found that almost half (47.8%) of a cohort of persons with RRMS (n = 46) diagnosed within the last six months, were found to meet criteria for cognitive impairment despite having relatively low neurologic disability. Cognitive changes have been shown to be present even before full diagnostic criteria for MS are met. After only one clinical attack representative of a demyelinating event in the CNS

(i.e., clinically isolated syndrome; Thompson et al., 2018), individuals were found to differ from age, sex, and education matched controls on cognitive tests of information processing speed and phonemic verbal fluency (Anhoque, Biccas-Neto, Domingues, Teixeira, & Domingues, 2013). Others have similarly identified cognitive changes early in MS, with the number of individuals with cognitive deficits increasing significantly in the first years of the disease; Reuter and colleagues (2011) followed individuals with clinically isolated syndrome for five years. Ninety-two percent of the sample met full criteria for MS at follow-up, and the frequency of impairments in at least one cognitive domain (e.g., memory, attention/information processing speed, executive functions) increased from 29% at baseline to 54% at five years. Zivadinov and colleagues (2001) found that a sample of individuals diagnosed with RRMS within the past five years similarly showed that 26.4% had cognitive impairment at baseline, with 52.8% of the sample demonstrating impairment after two years. Cognitive deficits early in the disease course have been shown to occur independent of the extent of neurologic disability, as rated by EDSS (Ruggieri et al., 2003), and occur over time even in individuals with little to no changes in neurologic disability (Amato et al., 2010).

As information processing speed is the most pervasive cognitive deficit in MS, Costa and colleagues (2017) reviewed a decade of literature discussing theories explaining why this deficit occurs. The most commonly used hypotheses were the “relative consequence model” (DeLuca, Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004) which posits that a fundamental processing speed deficit in MS underlies cognitive dysfunction in other areas, and the “limited time

mechanism" (Salthouse, 1996) which posits that when there are limits on the time available for processing, early cognitive operations may be completed too slowly, thereby leaving limited time for the remaining operations. Unfortunately, neither of these more popular models/mechanisms contribute to understanding the neuroanatomical correlates associated with deficits in processing speed (Costa et al., 2017).

Demyelination and CNS lesions are characteristic of MS, and conduction is slowed in the CNS when transmitting signals through a demyelinated pathway (McDonald & Sears, 1970). Even in aging adults without MS or other neurologic disorders, white matter lesions have been shown to account for age-related decreases in speeded cognitive tasks (Rabbitt et al., 2007). Persons with MS have long been known to have slower reaction time (RT) compared to control participants (Elsass & Zeeberg, 1983), however, understanding and accounting for these differences continues. Separating deficits due to cognitive processing speed or motor changes can be difficult when using a RT task. Stoquart-ElSankari and colleagues (2010) demonstrated that even in persons with MS with no motor difficulties on clinical exam, a motor deficit was still present on a finger tapping task. Research aimed at understanding the neuropathology of cognitive deficits in common domains other than speed, such as working memory, verbal and visual learning/memory, and executive functions, is still relatively limited. Most of this research has focused on finding in-vivo correlates of cognitive change using MRI.

1.6 MRI Correlates to Cognition in MS

MRI has become the primary diagnostic tool for MS, as it can identify structural changes over time related to MS neuropathology. Although persons with MS regularly receive MRI scans to monitor neurologic disease progression, the utility of MRI in understanding changes in cognitive function has been mixed. The term “clinical-radiological paradox” has been used to describe the weak association between the severity of clinical disability, including but not specific to cognitive impairment, and volume of white matter lesions imaged using MRI (Barkhof, 2002). As contributing factors to this paradox, Barkhof (2002) highlighted the limitations of EDSS, that structural imaging fails to capture functional loss or plasticity, and the narrow focus on measuring lesion volume instead of brain and spinal cord total volume.

Although MS has been classically conceptualized as a white matter disease (McKhann, 1982), studies examining whole brain volume have had some relative success compared to studies examining white matter lesions alone. Normalized brain volume has been found to be lower for cognitively impaired persons with MS compared to cognitively intact persons with MS and healthy controls (Hulst et al., 2013; Pravatà et al., 2017). Longitudinal work found brain parenchymal (i.e., white and grey matter functional brain tissue consisting of neurons and glial cells) volume loss to be significantly greater for persons with RRMS who cognitively worsened (i.e., decreased performance compared to baseline by 25% or more on two or more domains) over the course of two years, whereas there was no difference in lesion volumes between those who worsened, remained stable, or improved

(Zivadinov et al., 2001a). The brain parenchymal fraction [(white and grey matter volume/white matter, grey matter, and cerebral spinal fluid volume) x 100] has been employed as a measure of whole brain atrophy that is considered suitable for detecting small amounts of change in MS brain-disease progression (Rudick et al., 1999). Studies have shown cognitively impaired persons with RRMS to have a lower brain parenchymal fraction than those not cognitively impaired (Zivadinov et al., 2001b) and that the brain parenchymal fraction explains significant variance (10-15%) in cognitive performance, rendering lesion volumes uninformative, after accounting for age and premorbid intelligence on some tasks (Benedict et al., 2004).

Studies examining whole brain volume have coincided with increased work examining the grey matter specifically, given that atrophy of the grey matter has been demonstrated to occur early in MS disease course (Crespy et al., 2011). Hulst and colleagues (2013) found white matter volume did not differ between groups of cognitively impaired and unimpaired persons with RRMS/SPMS, however, decreased grey matter volume was found in the impaired group. Nocentini and colleagues (2014) similarly found associations between grey matter volumes and performance on standard neuropsychological tests in RRMS/SPMS, yet no significant correlations between white matter volumes and any of their neuropsychological tests. Calabrese and colleagues (2009) focused on lesion volume specifically, finding that white matter lesion volume did not differ between groups of cognitively impaired and unimpaired persons with RRMS, however, the impaired group had increased grey matter lesion volume and quantity. Yet others

have found both white and grey matter lesion volumes to be associated with cognitive function in RRMS/SPMS (Mike et al., 2011), and recent longitudinal work reported that annual gray matter atrophy rates in RRMS did not correlate with cognitive decline (Eijlers et al., 2019). Variability in the MS samples studied (e.g., three of the studies above had samples containing persons with RRMS and SPMS), despite the known differences in cognitive function between MS subtypes (Eijlers et al., 2019; Ruano et al., 2017; Aurélie Ruet, Mathilde Deloire, Julie Charré-Morin, et al., 2013), likely contributes to these variations in the literature.

Subcortical grey matter volume, specifically, has shown promising associations with cognitive function. Total subcortical grey matter measures typically include structures such as the amygdala, basal ganglia (i.e., caudate, putamen, pallidum, globus pallidus), hippocampus, and thalamus. Eijlers and colleagues (2019) found an association with subcortical grey matter atrophy and cognitive decline in the subset of persons with RRMS who converted to SPMS during the five years between baseline and follow-up testing. This is consistent with the work of Amato and colleagues (2004), who found that overall subcortical grey matter volume was significantly lower for cognitively impaired persons with RRMS compared to those who were cognitively intact and healthy controls. Additionally, among those in the cognitively impaired group, persons who had failed a greater number of cognitive tests had even lower subcortical grey matter volumes.

Among the subcortical grey matter structures, the thalamus appears to be particularly relevant to cognition. Bisecco and colleagues (2018) found that

thalamic volume remained the only significant predictor of information processing speed after controlling for age and volume of normal appearing grey matter. Batista and colleagues (2012) found a similar result, wherein the volume of both the thalamus and putamen predicted information processing speed performance when controlling for age, however, only putamen volume remained in the model when controlling for age and total neocortex grey matter volume. This suggests that the importance of the thalamus is closely tied to its widespread connections to the neocortex, whereas the putamen makes a stronger independent contribution to information processing speed. The putamen has been identified as the subcortical grey matter structure with the greatest rate of volume loss over time, across MS subtypes (Eshaghi et al., 2018). Benedict and colleagues (2009) found the thalamus and caudate to have the strongest correlations with tests associated with information processing speed and verbal learning/memory, with the hippocampus showing a weak association with the test associated with verbal learning. Pravatà and colleagues (2017) similarly found thalamus, caudate, and putamen volumes bilaterally and left hippocampus volume to differ between cognitively impaired and cognitively intact persons with MS. The nucleus accumbens (bilaterally) also differed between groups in this study, but not the amygdala or pallidum. Despite variation in study results, it appears clear that atrophy of the thalamus, caudate, putamen, and hippocampus play some role in cognitive impairments in MS.

1.7 Comorbidities and Common Symptoms That Affect Cognition.

As measures of disease severity in MS, such as EDSS and MRI measures of lesion burden, have had limited utility in explaining the variability in cognitive

deficits in MS (Amato et al., 2010; Ruggieri et al., 2003), research continues to search for additional explanations of cognitive changes. Two concurrent mental health conditions (i.e., comorbidities), depression and anxiety, have gained interest given that they both occur more frequently in persons with MS than in the general population (Marrie et al., 2015a) and have been shown to affect cognitive functioning in the general population. For example, a meta-analysis of 24 studies looking at cognition in individuals diagnosed with major depressive disorder found depressed individuals show decreased performance in the domains of executive functioning, memory, and attention compared to healthy control groups (Rock, Roiser, Riedel, & Blackwell, 2014). Gualtieri and Morgan (2008), who examined individuals with major depressive disorder as well as individuals with generalized anxiety disorder, found that both groups demonstrated a greater frequency of cognitive impairments (i.e., 19% and 21% for anxiety and depression groups, respectively) than their control group (i.e., 4%).

According to the World Health Organization (2017), the global population with depression and anxiety is 4.4% and 3.6% respectively, however, the prevalence of these conditions in population-based studies of MS ranges as high as 44.6% for anxiety and 58.9% for depression (Marrie et al., 2015a; Marrie et al., 2015b). Emerging research comparing MS to other immune-mediated inflammatory diseases suggests that the common pathophysiological processes (e.g., neuroinflammation) of these diseases is associated with the development of common mental health conditions such as depression/anxiety. Annual incidence rates of common mental health conditions were found to be almost double in

immune-mediated inflammatory disease populations compared to an age, sex, and location of residence-matched cohort (26.1 versus 15.1; Marrie et al., 2017). In addition, incidence rates of depression/anxiety have been found to be elevated in MS and other immune-mediated inflammatory diseases up to five years prior to diagnosis (Marrie et al., 2019) and may represent prodromal symptoms of MS (Disanto et al., 2018).

Symptoms of depression/anxiety have been found to explain variance in cognitive functioning in MS and other immune-mediated inflammatory diseases (Whitehouse et al., 2019), however, the exact profile of which symptoms affect which cognitive functions appears to vary among studies. Whitehouse and colleagues (2019) found current symptoms of anxiety to explain unique variance in tests associated with processing speed, verbal learning, and working memory, and symptoms of depression to explain unique variance on a test associated with processing speed. These relationships differed when looking at whether individuals met criteria for major depressive disorder or an anxiety disorder, whereby meeting criteria for anxiety disorder explained variance in processing speed but major depressive disorder was not associated with cognitive function. Only 10.2% of the MS sample met criteria for major depressive disorder while 19.9% self-reported a clinically significant quantity of depressive symptoms, likely contributing to the difference comparing current depressive symptoms to diagnoses. In addition to information processing speed, Morrow and colleagues (2016) found symptoms of depression/anxiety to be associated with visual memory. Visual memory was not assessed by Whitehouse and colleagues (2019).

Others have similarly found a connection between symptoms of depression/anxiety and decreased cognitive performance in MS (DiGiuseppe et al., 2018; Leavitt et al., 2019; Nunnari et al., 2015). A focus on these comorbidities remains of interest as they are considered “modifiable factors” for MS prognosis, given that treatments for symptoms of depression/anxiety exist. Although psychological and pharmacological treatments for depression have been validated in MS, the effect of these treatments on possible cognitive improvements has not been examined, and additional research on anxiety is needed (Fiest et al., 2016a).

Depression and anxiety in MS frequently co-occur with other symptoms, and symptom “clusters” have been described that include depression, anxiety, fatigue, and pain (Amtmann et al., 2015). Fatigue and pain are prominent symptoms in MS, although reported prevalence rates have varied widely for both symptoms: fatigue up to 78.2% (Fiest et al., 2016b), pain 29% to 86% (O’Connor, Schwid, Herrmann, Markman, & Dworkin, 2008). Pain has been shown to have a significant indirect effect on symptoms of depression in MS, whereby pain influences fatigue which influences depression (Amtmann et al., 2015). Persons with MS report pain sensations to interfere with their recreational activities, work, and ability to move around (Hadjimichael, Kerns, Rizzo, Cutter, & Vollmer, 2007). Although authors examining pain in the context of symptom “clusters” have found that pain is associated with perceived/subjective cognitive deficits in MS (Motl, Suh, & Weikert, 2010), there has been limited work demonstrating an effect of pain on objective cognitive performance in this population. Newland, Fearing, Riley, and Neath (2012) looked at a computerized measure typically considered to assess

processing speed (the Paced Auditory Serial Addition Test; PASAT) in 40 persons with RRMS, and found that pain severity did not correlate with impaired performance on the computerized measure. Yet a body of literature examining pain and cognition in other populations (e.g., chronic pain) supports a connection between pain and decreased cognitive performance (Moriarty, McGuire, & Finn, 2011). Visual and verbal memory, information processing speed, and executive functions have been shown to be affected in persons living with chronic pain. Moriarty and colleagues (2011) reported that attention is a cognitive domain of interest in chronic pain populations, given that pain is an "attention-demanding sensory process" (p. 390). Although the authors state that attention is well-studied in chronic pain, most articles discussed in their literature search included only a limited neuropsychological assessment of attention, such as Oosterman and colleagues (2011) who included only a cancellation task (i.e., Bourdon-Vos test; scan groups of dots and cross out all groups of four dots). Dick and Rashiq (2007) administered the more specialized Test of Everyday Attention, typically considered to assess sustained and selective attention as well as attentional switching, to persons with chronic pain. The authors found that short-term interventions resulting in pain reduction (e.g., somatic nerve blockade) did not result in an increase in cognitive performance. These results suggest that it is not necessarily an individual's current pain state that impacts cognitive functioning.

Persons with MS self-report their symptoms of fatigue to have a significant impact on their cognitive abilities (Fisk, Pontefract, Ritvo, Archibald, & Murray, 1994). Using objective cognitive testing, increased symptoms of fatigue have been

shown by some to be associated with lower cognitive functioning (Amato et al., 2010; DiGiuseppe et al., 2018), however, others have not found an association between symptoms of fatigue and cognitive function (Deloire et al., 2005; Hulst et al., 2013). Symptoms of depression and anxiety are often reported as highly correlated with fatigue in MS (Leavitt et al., 2019; Morrow et al., 2016), further complicating the relationship between fatigue and cognitive function. Hanken, Eling, and Hildebrandt (2015) reviewed the literature on fatigue and cognitive performance in MS, concluding that only performance on cognitive tasks involving two attentional processes were correlated with fatigue (i.e., vigilance and "alertness", labeled as orienting in subsequent studies discussed below).

1.8 Attention in MS

Attention is a multi-faceted and fundamental cognitive function that interacts with other cognitive abilities, such as memory (Chun & Turk-Browne, 2007). Working memory in particular is closely tied to attentional abilities. In his review titled the "Fundamental Components of Attention", Knudsen (2007) described working memory and attentional abilities as "inextricably inter-related" (p. 60). To what an individual attends determines what information enters working memory, and what is held in working memory depends on what was attended too. This is consistent with the influential model of working memory proposed by Baddeley (1992). Even though the model included three components of working memory, the main component was actually described as an "attentional-controlling system" (p. 255; i.e., the Central Executive).

Although slowed processing speed is reported as the primary cognitive change in MS, tests of processing speed often require attentional abilities. For example, decreases in sustained attention in MS have been shown to explain some of the difference between persons with MS and controls on speeded tasks (Stoquart-ElSankari et al., 2010). Many studies on cognition in MS potentially overlook changes in attention in this population. In their review of research on cognitive impairments in MS, Chiaravalloti and DeLuca (2008) explained that there is variability in which processes and tasks are labeled as attention-related, and factors such as fatigue are often not considered. For example, the Symbol Digit Modalities Test is one of the tasks most commonly used to assess information processing speed in MS (Benedict et al., 2016). Yet, Amato and colleagues (2010) described the Symbol Digit Modalities Test as “a test of complex attention and sustained concentration” (p.1479), and both Ruet and colleagues (2013) and Reuter and colleagues (2011) conceptualized the task as assessing attention and information processing speed. Macniven and colleagues (2008) sought to examine whether the commonly reported difference in RT between persons with MS and control participants on a Stroop Task were due to deficits in processing speed, executive functions, or selective attention, as poor Stroop Task performance has been attributed to one or more of these cognitive domains in the MS literature. Their study concluded that slowed processing speed was the reason for poor Stroop Task performance, highlighting that connections in the literature regarding task performance and reported cognitive domain(s) affected may not always be

correct. Differences in how the various aspects of attention are conceptualized and described creates difficulties in building a body of literature on the subject.

Posner and Petersen (1990) produced a model of three networks of attention based on existing behavioural evidence and neuroimaging research. The networks are: (1) orienting – the ability to prioritize sensory information by shifting attentional focus, for example, attending to a location in physical space or only one modality, (2) vigilance/alerting – establishing and maintaining an alert state in which the individual is *prepared* to detect and response to a stimulus, and (3) executive control – focal or conscious control of attention, including detecting and acknowledging a target, managing conflicting responses, and regulating attentional processes.

Twenty years later, after a boom of neuroimaging studies, the authors were able to show further support for their originally proposed networks and discussed additional processes, such as self-regulation and network efficiency (Petersen & Posner, 2012). Each of the three original networks corresponds to anatomically unique systems. The orienting network appears to function largely within the parietal cortex with connections to frontal areas such as the frontal eye fields and ventral frontal cortex. The vigilance/alerting network appears to rely on brain stem arousal, such as norepinephrine release from the locus coeruleus, and systems within the right cerebral cortex. Lastly, current evidence suggests there are actually two major components of the executive control network, a frontoparietal component which appears to operate within the lateral frontal and parietal regions, and a cinguloopercular component which appears to operate within the medial

frontal/cingulate cortex and anterior insula. These two components are thought to act relatively independently in coordinating top-down attentional control (Petersen & Posner, 2012). This variability supports that there are a number of processes at work within each of the three attention networks and assessment tools for these attention networks need to be able to capture the degrees of variability within networks.

Posner and Petersen's three network model has been used in various studies aiming to understand how attentional abilities are affected in MS, particularly following the development of the Attention Network Test (ANT; Fan, McCandliss, Sommer, Raz, & Posner, 2002). The ANT is a computerized assessment measure that can be administered in under 30 minutes and is designed to assess Posner and Petersen's three attention networks. Examinees are asked to press the right or left arrow key to indicate whether a target is pointing right or left. The target can appear in one of two locations, can be accompanied by cues to the target location or cues to when the target will appear, and can include either congruent or incongruent flankers. The three network scores are calculated based on differences in RT between the various conditions. The first cross-sectional study using the ANT in MS found the vigilance/alerting network to be negatively affected in MS compared to control participants, despite only two of the 57 RRMS participants meeting criteria for cognitive impairment on standard neuropsychological tests (Urbanek et al., 2010). On the ANT, impairment on the vigilance/alerting network indicates that persons with MS do not obtain as much of an RT benefit from warning cues as control participants. The orienting and

executive control networks did not differ between the MS and control groups. This pattern has been found in persons recently diagnosed with MS that have a low neurologic disability based on EDSS (Crivelli et al., 2012). Symptoms of depression were not found to be associated with vigilance/alerting network performance in either study. Although there were no overall differences in the executive control network between groups, there was an interaction. Persons with MS experienced interference in the executive control network, whereby they benefitted less from cues when the cues were followed by incongruent flankers. This deficit in response inhibition following a cue did not occur in control participants, as they were found to benefit from cues regardless of whether the flanker that followed was congruent or incongruent (Crivelli et al., 2012; Urbanek et al., 2010).

Using a successive version of the ANT, the ANT-Interactions (ANT-I; Callejas, Lupiáñez, Funes, & Tudela, 2005), which employed separate sensory modalities for vigilance/alerting and orienting networks (auditory and visual, respectively), Omisade and colleagues (2012) did not find a difference in the vigilance/alerting network between persons with MS and controls. However, the interaction was still present: a deficit in response inhibition following an incongruent cue in the MS group only. This effect was conceptualized by the authors as the vigilance/alerting network affecting the executive control network differently in persons with MS versus control participants. This same pattern of results was replicated by other studies by the same group (Ishigami, Fisk, Wojtowicz, & Klein, 2013; Wojtowicz, Omisade, & Fisk, 2013), although Wojtowicz and colleagues

(2013) also found an overall difference in the executive control network between MS and controls.

These three studies (Ishigami et al., 2013; Omisade et al., 2012; Wojtowicz et al., 2013) relied on difference scores between performance conditions, which control for within-group differences in information processing speed but do not control for between-group differences (i.e., between-group differences in performance on the measure used as a baseline for calculating an individual's difference scores). Roth and colleagues (2015) compared methods of analyzing the ANT, and demonstrated that the pattern of attentional deficits identified using the ANT differed depending on how the results were analyzed. The authors argued that residualized and proportional scores, which use regression and division respectively to account for between-group differences in RT, are superior to difference scores as they account for between-group differences. Yet their results between methods were mixed. When using difference scores, a disparity in the executive control network was identified. When using residualized or proportional scores, the executive control network was no longer significantly different between groups. Instead, differences in the vigilance/alerting network emerged, consistent with Urbanek and colleagues (2010) and Crivelli and colleagues (2012) who also used proportional and residualized scores, respectively. Although both of these authors identified a vigilance/alerting network effect in RRMS, Roth and colleagues (2015) found that only SPMS, not RRMS, differed from controls in vigilance/alerting network performance. Results regarding the orienting network were less clear, with no differences identified between groups using difference or residual scores yet a

difference emerged when using proportional scores. Roth and colleagues (2015) succeeded in highlighting the inconsistency in results using the ANT in MS populations. No further studies using the ANT to understand attention network function in persons with MS have surfaced since the work of Roth and colleagues (2015).

The variable results when using the ANT in MS populations demonstrated by Roth and colleagues (2015) is consistent with psychometric criticisms of using the ANT in the general population. Macleod and colleagues (2010), who examined data from 15 studies who administered the ANT (n = 1,129 individuals), concluded that there is low reliability for the vigilance/alerting and orienting networks. The authors also demonstrated that the networks measured by the ANT are not necessarily independent. Although this is likely consistent with interaction in the attention networks described by Petersen and Posner (2012), inter-network correlations do negatively affect psychometric reliability. In addition, the ANT relies on a single difference score to represent each network, going against the recommendations of Sumowski and colleagues (2018) – "key priorities" for research in cognition in MS, who highlighted the need for composite variables to represent cognitive functions in MS more accurately.

1.9 Computerized Cognitive Testing

Despite technological advancements in many other areas of health care, most clinical neuropsychological assessments continue to rely on paper-and-pencil tests that require long appointments with skilled test administrators. This results in limited availability of neuropsychological evaluations. Miller and Barr

(2017) expressed in their commentary, “The Technology Crisis in Neuropsychology”, that cognitive testing stands to benefit from using technology to better capture human behaviour. Computerized measures allow for built-in standardization of administration, automated scoring, and fewer limitations on who can administer the measure.

Researchers in the field have argued that computerized assessment measures for the detection and monitoring of cognitive changes and deficits in MS could increase the access to cognitive testing in this population (Lapshin, O'Connor, Lanctôt, & Feinstein, 2012). Two groups have conducted literature reviews of computerized batteries that have been used to assess cognitive functioning in MS (Lapshin et al., 2012; Wojcik et al., 2019). The earlier review, by Lapshin and colleagues (2012), reported that while computerized assessments existed to differentiate persons with MS from controls, validity and reliability studies were lacking. More recently, Wojcik and colleagues (2019) identified all computerized tests used to assess cognition in MS and reported on the availability of psychometric data for each test in four areas of interest: (1) test-retest reliability, (2) discriminant validity, (3) ecological validity, and (4) concurrent validity. The review examined each test, and therefore collections of cognitive tests packaged into an assessment battery were broken down into their individual tests. The highest number of individual tests was reported for measuring processing speed (n = 44), with attention, working memory, and episodic memory each having half the number of tests available (n = 23, 22, and 21, respectively). The fewest number of tests were identified to assess executive functioning (n = 14). Within the tests

that were used to assess attention, only three of the 23 had psychometric data in all four areas of interest. Two of these tests designed to assess attention were only one piece of larger testing batteries: the Cognitive Drug Research battery (Edgar et al., 2011) and Neurotrax (Achiron et al., 2007). Both test batteries are collections of cognitive tests that assess multiple cognitive domains affected in MS, of which attention is only one of domains examined. Although the ANT was listed as having psychometric data in all four areas of interest, it was not included in the list of tests meeting these criteria as the psychometric data available for the ANT were mixed (i.e., both poor and adequate reliability has been demonstrated in a category) or non-significant (e.g., was not associated with relevant patient outcomes or standard neuropsychological tests).

1.10 Intra-individual Variability

The majority of computerized cognitive tasks rely on mean-level RT differences between groups to evaluate performance. In addition to mean-level RT differences, within-subject variability of RT on computerized tasks has been explored as a possible measure of cognitive abilities. Although this literature has been developing in other populations, limited work exists examining within-subject variability of RT in MS. Within-subject variability, or intra-individual variability (IIV), is an indicator of the stability of an individual's performance over time: increased IIV represents poor consistency in an individual's RT. IIV accounts for between-group differences in RT and within-session learning effects in its calculation, by parceling out the variation due to "group" and "trial" (Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000). IIV has been shown to increase with age in

adult populations (Williams, Hultsch, Strauss, Hunter, & Tannock, 2005) and existing work suggests that it is a “behavioural indicator of CNS integrity” (p. 475, MacDonald, Nyberg, & Bäckman, 2006). IIV has been found to reflect neurologic dysfunction in a variety of clinical populations and is relatively unaffected by somatic disturbances (e.g., pain); Hultsch and colleagues (2000) found IIV on several RT tasks to be greater in individuals with dementia, compared to those with arthritis (i.e., joint pain) and controls. Other neurologic conditions have been shown to have increased IIV compared to controls, such as traumatic brain injury (Stuss, Murphy, Binns, & Alexander, 2003) and autism spectrum disorder (Geurts et al., 2008). IIV has additionally been found to be more sensitive to cognitive changes than accuracy or speeded measures in individuals with breast cancer (Collins, Widmann, & Tasca, 2018).

IIV, which accounts for between-group RT differences, could be of particular benefit to research on computerized cognitive testing in MS – a population where baseline differences in RT must be accounted for and CNS integrity is affected. Persons with MS have been shown to have increased IIV (i.e., more variability) compared to controls, even when the overall slowed RT of persons with MS is considered (Wojtowicz, Berrigan, & Fisk, 2012; Wojtowicz et al., 2013). The measure has demonstrated stability across testing sessions in MS and is less susceptible to practice effects compared to commonly used mean-RT variables (Wojtowicz, Ishigami, Mazerolle, & Fisk, 2014). Increased IIV on computerized tasks of information processing speed is associated with decreased functional connectivity of white matter (Mazerolle, Wojtowicz, Omisade, & Fisk, 2013) and

decreased default mode network connectivity (Wojtowicz, Mazerolle, Bhan, & Fisk, 2014). The measurement of IIV shows promise as a sensitive indicator of changes in cognitive functioning in MS and should be examined when using computerized testing measures in this population.

1.11 The Dalhousie Computerized Attention Battery

The Dalhousie Computerized Attention Battery (DalCAB) is a novel computerized measure of attention developed at Dalhousie University (Nova Scotia, Canada). It includes eight computerized tasks, selected given their common use in cognitive research and existing validation for assessing the different aspects of attention. Given that attention is a fundamental cognitive function that interacts with and effects other cognitive abilities, proper assessment of attentional abilities is necessary for understanding attention and how it changes in different populations. Valid and reliable assessment of cognitive functioning is the first step in developing rehabilitation programs and pharmaceutical treatments to slow or prevent loss of cognitive functions.

Although Posner and Petersen (1990) continue to demonstrate research support for their model of conceptualizing attention networks (Petersen & Posner, 2012), the only measure designed to assess these attention networks, the ANT/ANT-I, has several limitations. Initial validation work of the DalCAB by Jones and colleagues (2015) has identified the measure to have a nine factor structure that aligns with the three networks of attention proposed by Posner and Peterson (1990): Vigilance/alerting, orienting, and executive control. Some interaction between the networks was also noted by Jones and colleagues (2015), such as

one factor that appeared to be associated with both vigilance and executive control as it included variables associated with proactive interference and also maintaining vigilance over time. In subsequent work, Jones and colleagues (2016), confirmed that the tasks produced the expected results in healthy controls and assessed retest reliability. The DalCAB was designed such that aspects related to the networks of attention are assessed repetitively within the same battery, providing multiple scores of the same attentional network instead of relying on a single score (such as the difference scores used by the ANT). The DalCAB includes tasks that allow for the assessment of information processing speed (i.e., a simple RT task) as well as the networks of attention. The DalCAB has been used to assess cognitive function or cognitive change in other populations, such as post-operative patients who required general anesthesia (elective or major non-cardiac related surgeries) and individuals with Parkinson's disease (Drake, 2019; Sardiwalla, Eskes, Bernard, George, & Schmidt, 2019). To date, no studies have administered this computerized battery to persons with MS, however, its ease of administration and ability to control for differences in processing speed make it a potentially promising tool to assess attentional abilities in MS. This is especially relevant given the lack of existing valid and reliable tests of attention used in this population. As a computerized assessment measure, IIV can be calculated for all DalCAB tasks, providing an additional measure for cognitive performance.

1.12 Summary and Aims

Multiple sclerosis (MS) is a neurodegenerative disease highly prevalent in Western countries such as Canada. There is currently no cure for MS and

individuals live for decades with the disorder, making research on factors that impact life with MS of particular importance. Technological advancements such as MRI have improved the process of diagnosing MS, allowing individuals to be identified earlier and more accurately. New disease modifying drugs are slowing disease progression. These changes mean there are more people diagnosed with MS who are in the milder stages of disease, and people remain in those stages for longer.

Although neurologic disability due to MS is typically captured by a measure biased toward physical disability (i.e., the EDSS), over the last 30 years cognitive impairments have become a widely recognized issue. Cognitive deficits are highly prevalent in MS and can occur early in disease course. They can be among the most limiting changes in individuals rated as having low neurologic disability. Cognitive changes in the domains of information processing speed, working memory, verbal and visual learning/memory, complex attention, and executive functions have been identified. In trying to understand why some persons with MS develop cognitive impairments and some do not, research has endeavoured to account for the variability between individuals. Attempts to find neural correlates of cognitive dysfunction on MRI have found white matter lesions to inconsistently explain little of the variability between individuals. Other structural measures such as brain parenchymal volume, grey matter volume, and volumes of subcortical grey matter structures such as the thalamus, putamen, caudate, and hippocampus, appear to show greater promise. Additional factors that have been

shown to affect cognitive functioning are symptoms of depression, anxiety, fatigue, and pain – all of which are common in MS.

Attention is a fundamental cognitive function which plays a role in many tasks conceptualized as assessing other cognitive domains. Posner and Petersen developed a model of three attention networks based on behavioural and neuroimaging research. These three attention networks (orienting, vigilance/alerting, and executive control) have been assessed in MS using variations of one computerized measure (i.e., the ANT/ANT-I), however, limitations of that measure have led to inconsistent results. Although two other individual tests have been used to assess attention in MS, they are included within larger test batteries measuring multiple cognitive domains and do not assess broad attention network function. Further work is needed to clarify the role of attention in cognitive functioning in MS.

The current research study used a novel computerized measure, the DalCAB, which includes eight tasks that assess Posner and Petersen's three networks of attention. Although it has been validated in other populations, the DalCAB has not been used to examine cognitive function in persons with MS. Given that few computerized assessment measures of attention have been used in MS, and those used either (1) have methodological limitations such as producing only a single score for each network or (2) do not assess attention in depth, a new option for measuring attention in MS is needed. Using a measure based on Posner and Petersen's model of attention networks, which can be mapped onto unique neuroanatomical networks, has additional advantages for connecting cognitive

performance to MRI correlates in MS. Given that the DalCAB is a computerized measure, IIV can be calculated for each task. This measure has been reported to reflect CNS integrity and has shown promise as a more sensitive indicator of cognitive changes in MS compared to standard neuropsychological measures and mean-level RT differences. The early and thorough assessment of cognitive impairments in MS may be beneficial for predicting prognosis and for making decisions regarding treatment intensity early in the disease course. Assessment of this type may also be beneficial for monitoring disease progression over time and for measuring the efficacy of treatments (e.g., pharmaceutical) or interventions (e.g., cognitive rehabilitation and training).

The current study has four main aims:

(1) To examine whether networks of attention are affected in persons with MS otherwise thought to have low neurologic disability based on their EDSS and to validate a novel computerized measure of attention, the DalCAB, in an MS population.

(2) To examine whether differences in performance based on mean-level RT on the DalCAB, or IIV on the DalCAB, are detected in persons with MS who are not impaired on standard neuropsychological tests used clinically.

(3) To examine whether symptoms of anxiety, depression, pain, and fatigue account for variation in attention network performance and IIV in persons with MS.

(4) To examine whether structural brain measures on MRI are associated with attention network performance in MS, as measured by the DalCAB, or IIV on the DalCAB.

Although the methods for aims (1) to (3) are described in *Chapter 2* below, the methods for the MRI sub-study, which addresses aim (4), are discussed in detail later in *Chapter 6*.

Chapter 2. Method

2.1 Participants

MS Group.

Persons with MS were recruited from the Dalhousie MS Research Unit in Halifax, Nova Scotia, Canada. The Dalhousie MS Research Unit is an integrated clinical care/research clinic which is the only specialized MS ambulatory care clinic in Nova Scotia and the primary provider for provincially funded MS disease modifying drugs since 1998. As part of the clinic's standard of care, persons who attend the Dalhousie MS Research Unit are asked whether they provide consent to have their personal health information accessed to assess their eligibility for local research studies. This standard was implemented in 2013. As of January 2019, 96.6% of the 1,910 persons approached had provided consent. Most patients of the Dalhousie MS Research Unit are assessed annually and data on their MS status are obtained: EDSS, MS subtype, date of symptom onset, date of MS diagnosis, current medications, and history of relapses since last visit. Information on other medical comorbidities and demographic characteristics is recorded.

Persons with upcoming clinical appointments were screened by Dalhousie MS Research Unit staff for eligibility in the current study based on their most recent clinical record. Persons who appeared to be eligible were informed of the study by clinic staff at their appointment. Those who were interested in the current study and agreed to be contacted by a member of the research team were given a self-report questionnaire designed for the current study to assist in confirming their

eligibility. The first 53 MS participants enrolled did not complete the self-report questionnaire designed for the current study as it had not-yet been added to the study procedures.

Persons with MS were included in the study if they had a clinically definite diagnosis of RRMS as determined by their attending clinician at the Dalhousie MS Research Unit. Although patients in the clinic may have received their MS diagnosis prior to the release of the most recent diagnostic criteria (2017 revisions of the Macdonald criteria; Thompson et al., 2018), all met criteria for clinically definite MS as determined by their attending clinician. Only persons with RRMS were included given that RRMS is the most common MS subtype and cognitive deficits have been shown to differ in progressive MS (Ruano et al., 2017; Aurélie Ruet, Mathilde Deloire, Julie Charré-Morin, et al., 2013; Zakzanis, 2000). In addition, persons with MS were only included if they had been relapse-free for at least three months prior to participation and had no more than moderate levels of neurologic disability as determined but their most recent neurological examination (i.e., EDSS $\leq$ 6). Patients between ages 20 to 60 years (inclusive) were approached. No persons with pediatric onset MS were included (i.e., diagnosed prior to 18 years of age). Patients were excluded from the study if they had non-cognitive deficits (i.e., insufficient visual acuity or impaired dexterity) that would impede performing the cognitive tasks, described later. Insufficient visual acuity was defined as having corrected vision <20/40 in their better eye using the standard Snellen eye chart (20/20 representing normal vision). Impaired dexterity was defined as taking > 35 seconds to complete the Nine-Hole Peg Test with their

dominant hand (i.e., the speed at which an individual can place nine pegs into a 3x3 series of holes; Kellor, Frost, Silberberg, Iverson, & Cummings, 1971). These two tests were generally available among patient's clinical records, however, if not available, these tests were completed by clinic staff prior to enrolling the individual in the current study.

Persons with MS were also excluded if they had comorbid conditions that were likely to have a significant impact on their cognition. Excluded conditions included having a diagnosis or medical history of: a comorbid neurologic disorder other than MS (e.g., dementia, epilepsy, Parkinson's), a diagnosed learning disability, a previous head injury with loss of consciousness, a sub-optimally managed psychiatric disorder (e.g., anxiety, depression, bipolar; as determined by their attending clinician at the Dalhousie MS Research Unit), or recent treatment with medications known to have major adverse impacts on cognition (e.g., chemotherapy). Persons with MS on drugs for the treatment of MS and associated symptoms were not excluded, even though some of these drugs have been shown to have negative effects on cognitive functioning (e.g., pregabalin for the treatment of pain and spasticity; Salinsky, Storzbach, & Munoz, 2010). The current study recorded whether persons with MS were on first, second, or third-line treatments for their MS, but not the exact drug they were taking. Lastly, patients were excluded if they were unable to provide informed consent for any reason. Participants in the MS group were reimbursed for their parking costs during the study visit.

One hundred and ten persons with MS completed the current study. Six persons in total were removed from analyses. See Figure 2 for flow diagram of

excluded participants. Two of the participants were removed from analyses to increase the uniformity of the MS group, as they were the only participants with EDSS scores greater than 4.5. Including only participants with an EDSS of 4.5 or less was considered a clinically meaningful cut-point, as individuals who meet this criterion are not regularly limited in their daily activities by their ability to ambulate (See Table 2). As such, changes in cognition may represent one of the more functionally limiting changes for individuals with levels of neurologic disability at this level or lower. The description of all 20 possible EDSS scores (i.e., 0 to 10 at 0.5 increments) is free and readily available online, see US Department of Veteran's Affairs (2018), accessed 26 May 2020 via https://www.va.gov/MS/Professionals/diagnosis/Kurtzke_Expanded_Disability_Status_Scale.asp.

Table 2. Comparison of EDSS Endpoints.

EDSS	**Description**
4.5	"Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance […] able to walk without aid or rest greater than 300 meters"
5.0	"Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions) […]"

Note. From US Department of Veteran's Affairs (2018); Portion of EDSS descriptions talking about Functional Systems is excluded.

Participants in the final MS group (*n* = 104) were mainly female (87.5%), ranged in age from 21 to 60 years (*M* = 46.0 years), and had from 11 to 19 years of education (*M* = 14.6 years). Levels of neurologic disability as determined by EDSS were generally low, as the majority (81.7%) of the MS group had EDSS scores of 2.5 or less (*M* = 1.9; *Interquartile range* = 1.5 to 2.5). An EDSS of 2.5 represents "minimal disability in two Functional Systems" (US Department of

Veteran's Affairs, 2018). Years since MS onset ranged from 0 years (i.e., participant was diagnosed the same year they participated in the current study) to 37 years (*M* = 13.3; *Interquartile range* = 7 to 18 years). Most MS participants were treated with disease modifying drugs for their MS at the time of the study (81.7%; *n* = 85). Of those treated with disease modifying drugs, 68.3% (*n* = 71) were on a first line treatment and 13.5% (*n* = 14) were on a second line treatment. See Table 3 for participant characteristics.

Control Group.

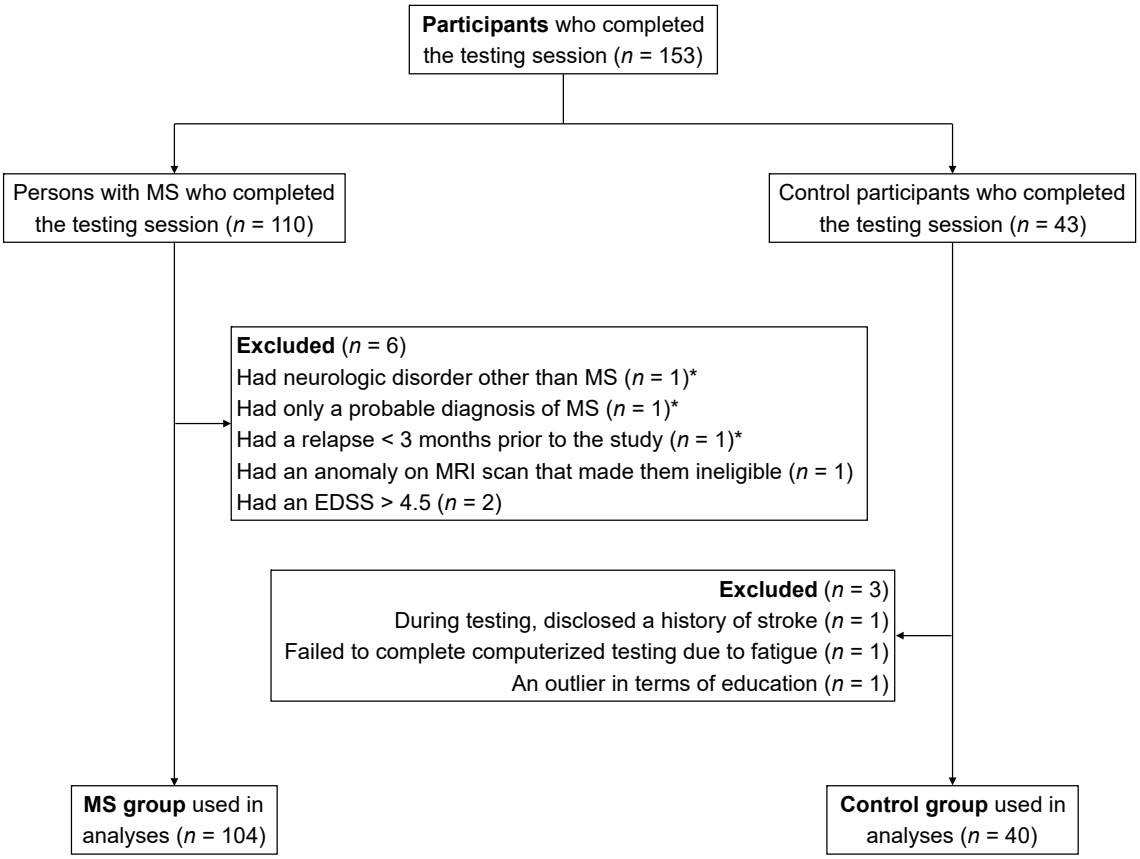
Healthy adults were recruited from the community via online advertisements (i.e., Kijiji and Facebook), posters, and word-of-mouth. All interested individuals completed a screening questionnaire to confirm their eligibility for the current study and determine whether they were a match to the MS group in terms of age, sex, and years of education. The majority of the MS group had been enrolled in the current study prior to commencing recruitment of the control group. To facilitate the matching process for age, MS participants were grouped into bins of 5 years and control participants were recruited so as to have the same percentage of individuals in each bin.

Individuals in the community sample were excluded from the study based on the same criteria used for the MS group, with some exceptions: (1) community members were not formally tested for non-cognitive deficits such as poor visually acuity and were instead asked to self-report if they had these deficits on the screening questionnaire, (2) community members were excluded if they had been diagnosed or treated for a psychiatric disorder such as depression or anxiety, (3)

community members were excluded if they had a diagnosis of MS or a first-degree relative (e.g., parent, sibling) with MS, given that first-degree relatives have an increased risk of developing the disorder (Ramagopalan, Dobson, Meier, & Giovannoni, 2010). The first 30 control participants to complete the study were entered in a draw to win one of 10 $50 VISA gift cards. Due to subsequent difficulties completing recruitment, the remaining 13 control participants each received a $50 VISA gift card.

Forty-three community members participated in the current study. Three participants were excluded from the analyses. See Figure 2 for flow diagram of excluded participants. Community members in the control group (n = 40) did not differ from the MS group in terms of age or years of education using independent sample's t-tests (equal variances not assumed). The groups did not differ in terms of their percentage of female participants using Pearson Chi-Squared. See Table 3 for participant characteristics and statistical comparisons.

Figure 2. Flow of Excluded Participants.



Note. *Participants were enrolled in the study prior to adding a self-report questionnaire to assist in confirming eligibility. These details were missed when they were screened into the study based on their most recent clinical visit at the Dalhousie MS Research Unit.

Table 3. Participant Characteristics.

Characteristic	MS Group	Control Group	Statistical Comparisons
N	104	40	
Sex, n (%)			
Female	91 (87.5)	36 (90.0)	$X^2(1) = .173$, $p = .677$
Male	13 (12.5)	4 (10.0)	
Age, mean (SD)	47.0 (8.6)	49.4 (9.6)	$t(64.5) = -1.380$, $p = .172$
Years of education, mean (SD)	14.6 (1.8)	15.1 (1.5)	$t(87.1) = -1.706$, $p = .092$
First Language, n (%)			
English	100 (96.2)	37 (92.5)	
Other	2 (2.0)	3 (7.5)	
Missing data	2 (1.9)	0 (0)	
Right-handed, n (%)	91 (87.5)	33 (82.5)	
EDSS score, mean (SD)	1.9 (1.0)	NA	
Years since onset, mean (SD)	13.3 (8.8)	NA	
Years since diagnosis, mean (SD)	10.6 (7.8)	NA	
On a disease modifying drug, n (%)	85 (81.7)	NA	

2.2 Measures

All participants completed standardized neuropsychological tests, questionnaires, and an experimental battery of tests assessing attention.

Test Selection.

Standardized neuropsychological tests were selected for the current study based on published recommendations for cognitive testing in MS, described below. The Symbol Digit Modalities Test total score, the five immediate recall trials of the

California Verbal Learning Test – Second Edition, and the three immediate recall trials of the Brief Visuospatial Memory Test – Revised were selected by a committee of European and American neurologists and neuropsychologists to comprise the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS; Langdon et al., 2012). These tests were selected by the committee as they best met the following considerations: (1) assess deficits commonly seen in MS, (2) have strong psychometric properties, and (3) respect the restrictions of clinical settings such as time constraints and limited access to assessors with neuropsychological training. The BICAMS was included among the suggested tests validated for MS populations in the most recent consensus recommendations for cognitive screening in MS (Kalb et al., 2018), and recent work has validated a tablet version of the BICAMS which may be easier to integrate into a clinical setting (i.e., less training to administer, specialized testing forms not required, shorter administration time, computerized scoring; Beier et al., 2020).

The current study included two additional tests to the BICAMS battery: Letter Number Sequencing (used to assess working memory) and the Controlled Oral Word Association Test (used to assess verbal fluency). Working memory deficits have been argued to play a prominent role in cognitive impairments in MS (Berrigan et al., 2013), interacting with and contributing to impairments in processing speed (Lengenfelder et al., 2006). Letter Number Sequencing was selected because it has previously been found to be sensitive to detecting working memory deficits in the persons with MS with relatively low neurological disability (Berrigan et al., 2013). Verbal fluency has been shown to be affected in persons

with MS within the first year following diagnosis (DiGiuseppe et al., 2018). The Controlled Oral Word Association Test has been selected as the verbal fluency measure of choice in a variety of cognitive screening batteries in MS, such as the Brief Neuropsychological Battery (Rao, 1990) and the Minimal Neuropsychological Assessment in MS Patients (Benedict et al., 2002).

The Wechsler Test of Adult Reading is considered to be an estimate of pre-morbid (i.e., relatively resistant to brain disease) functioning, and was selected for the current study because its large normative sample (*n* = 1,134) allows for the computation of age-adjusted standard scores (Wechsler, 2001). This measure was included in the current study in case participant groups (i.e., MS versus control) were not able to be matched on their level of education, in which case this measure could be used as a covariate in analyses. See Table 4 for description of neuropsychological test variables used in the current study.

2.2.1 Standardized Neuropsychological Tests – Brief International Cognitive Assessment for Multiple Sclerosis

Symbol Digit Modalities Test (SDMT).

Participants view lines of arbitrary symbols and are asked to match numbers to the symbols according to a legend provided at the top of the page. They are instructed to say their responses aloud to the examiner as quickly as possible. A participant's total score is the number of correct symbol-to-number matches completed in 90 seconds (SDMT Total). The SDMT (Smith, 2002) is typically considered to assess an individual's processing speed.

California Verbal Learning Test – Second Edition (CVLT–II).

Participants are read aloud a list of 16 nouns (belonging to four semantic categories, e.g., “animals”) and asked to repeat back as many of the words as they can remember (CVLT-II Trial 1). This sequence is repeated over five learning trials (CVLT-II Total Immediate Recall), followed by one trial with a distractor word list. Participants are subsequently asked to recall the entire original word list from memory (CVLT-II Short Delay Free Recall), then, they are cued as to each of the four semantic categories (CVLT-II Short Delay Cued Recall). After a 20-minute delay, participants are again asked to recall the word list without cues (CVLT-II Long Delay Free Recall) and to recall the word list with the category cues (CVLT-II Long Delay Cued Recall). The CVLT-II (Delis, Kramer, Kaplan, & Ober, 2000) is typically considered to measure an individual’s verbal learning and memory.

Brief Visuospatial Memory Test – Revised (BVMT–R).

Participants are briefly shown a page with six abstract geometric figures (2x3 array). Once the page is taken away, individuals are asked to draw the figures accurately and in the correct location. This process is repeated for three learning trials (BVMT-R Total Immediate Recall). After a 25-minute delay, participants are asked to draw the figures from memory (BVMT-R Long Delay Free Recall). The BVMT-R (Benedict, 1997) is typically considered to measure an individual’s visual learning and memory.

2.2.2 Standardized Neuropsychological Tests – Additional Measures

Controlled Oral Word Association Test (COWAT).

Participants are asked to list as many words that they can think of in 60 seconds all beginning with a particular letter (i.e., F, A, and S; COWAT Phonemic Total) and then are asked to do the same with words belonging to a semantic category (i.e., “animals”; COWAT Semantic Total). There are three phonemic fluency trials and one semantic fluency trial. The COWAT (Benton & Hamsher, 1976) is typically considered to measure verbal fluency.

Letter-Number Sequencing (LNS).

Examinees are read increasing larger series of numbers and letters. For each series, they are to reorder and repeat the items by listing the numbers first (from lowest to highest) followed by the letters (in alphabetical order). A participant’s total score is the number of series they are able to repeat correctly (LNS Total). LNS is a subtest of the Wechsler Adult Intelligence Scale – Third Edition (The Psychological Corporation, 1997) and is typically considered to measure an individual’s working memory capacity.

Wechsler Test of Adult Reading (WTAR).

Participants are asked to read a list of 50 words aloud. These words largely have atypical spellings that do not conform to standard phonetic rules, and therefore require prior familiarity with the words in order to pronounce them correctly. A participant’s total score is the number of words they are able to read correctly (WTAR Total). The WTAR (Wechsler, 2001) is typically considered to

estimate an individual's premorbid level of cognitive functioning (i.e., cognitive functioning prior to the onset of injury or disease).

Table 4. Description of Neuropsychological Test Scores.

Neuropsychological Variable Label	**Description**
SDMT Total	Symbol Digit Modalities Test; Total correct responses
CVLT-II	California Verbal Learning Test – Second edition
Trial 1	Total correct responses on the first learning trial
Total Immediate Recall	Total correct responses across the five learning trials
Short Delay Free Recall	Total correct responses on the first free recall trial
Short Delay Cued Recall	Total correct responses across the first four cued recall trials
Long Delay Free Recall	Total correct responses on the last free recall trial, administered after a 20-minute delay
Long Delay Cued Recall	Total correct responses across the last four cued recall trials, administered after a 20-minute delay
BVMT-R	Brief Visuospatial Memory Test – Revised
Total Immediate Recall	Total correct responses across the three learning trials
Long Delay Free Recall	Total correct responses on the free recall trial, administered after a 25-minute delay
COWAT	Controlled Oral Word Association Test
Phonemic Total	Total words listed across the three phonemic category trials
Semantic Total	Total words listed on the semantic category trial
LNS Total	Letter-Number Sequencing; Total number of series that were correctly repeated
WTAR Total	Wechsler Test of Adult Reading; Total number of words correctly read aloud

2.2.3 Self-Report Questionnaires.

Fatigue Impact Scale (FIS).

The FIS (Fisk, Ritvo, et al., 1994) quantifies the extent to which fatigue has been a problem for the individual in the past four weeks. The FIS was developed and validated for use in MS (Fisk, Pontefract, et al., 1994). Individuals rate 40-items on a five-point scale ranging from zero (“No Problem”) to four (“Extreme Problem”), for a total maximum score of 160.

Hospital Anxiety and Depression Scale (HADS).

The HADS (Zigmond & Snaith, 1983) screens for symptoms of depression and anxiety in the past week. Individuals provide the 14 items a score from zero to three, and separate total scores are obtained for the depression (HADS-D; seven items) and anxiety items (HADS-A; seven items). The HADS was one of the two recommended screening measures included in the most recent consensus recommendations for cognitive screening and management in MS (Kalb et al., 2018). When compared to other self-report screening measures (e.g., Patient Health Questionnaire; Kessler-6 Distress Scale) in a sample of 253 persons with MS, the HADS-A provided the best estimate of the prevalence of anxiety when compared to a standardized semi-structured diagnostic interview (Marrie et al., 2018). In the same sample, the HADS-D was a close-second at estimating the prevalence of depression when compared to a standardized semi-structured diagnostic interview, beat only by the Kessler-6 Distress Scale.

For use in the general population, scores of 11 or greater on the HADS-A or HADS-D are considered indicative of clinically significant symptoms of

depression and/or anxiety (Zigmond & Snaith, 1983). However, some symptoms of MS can overlap with symptoms of depression and anxiety. While a previous validation of the HADS for persons with MS proposed a cut-off score of eight for both the HADS-A and HADS-D (Honarmand & Feinstein, 2009), Marrie and colleagues (2018) demonstrated that a higher score of nine for the HADS-A achieves a better balance of sensitivity and specificity. Thus, in the current study, in the MS group a cut-off of eight was used for the HADS-D and nine for the HADS-A to identify persons with MS who had clinically significant depression and/or anxiety.

Health Utilities Index (HUI).

The Mark III version of the HUI (Furlong, Feeny, Torrance, & Barr, 2001) is a 15-item multiple choice questionnaire which quantifies health-related quality of life in eight health dimensions: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. From these, a single value is then calculated which represents an individual's health state across the eight health dimensions. This *single attribute utility score* ranges from zero (i.e. equivalent to death) to one (i.e. perfect health). When the HUI was compared to two other commonly used healthy utility measures in a sample of 187 persons with MS, the HUI had the highest concordance with clinical measures (e.g., EDSS) and demonstrated the highest test re-test reliability (Fisk et al., 2005).

Medical Outcomes Study – Pain Effects Scale (MOS-PES).

The MOS-PES was derived from the MOS Pain Measures (Stewart & Ware, 1992) and was modified specifically for person's living with MS as part of the

National MS Society (USA) Health Related Quality of Life Inventory (Ritvo et al., 1997). Individuals rate the extent to which pain and other unpleasant sensations due to MS (e.g., tingling, burning) have interfered with their everyday life in the past four weeks. The amount of interference with their mood, ability to walk/move around, sleep, complete normal work, recreational activities, and enjoy life are rated on a five-point scale ranging from one (“Not at All”) to five (“To an Extreme Degree”). The total score on the questionnaire is calculated by adding the ratings in all six areas.

2.2.4 Experimental Neuropsychological Assessment Measures.

Dalhousie Computerized Attention Battery (DalCAB).

The DalCAB is a novel computerized battery developed and validated by Jones and colleagues (2015; 2016) at Dalhousie University (Halifax, Nova Scotia). The DalCAB requires approximately 40-50 minutes to complete and includes seven tests of attention: (1) Simple Reaction Time, (2) Go-No-Go, (3) Choice Reaction Time, (4) Dual Task, (5) Vertical Flanker, (6) Item Memory, and (7) Visual Search. Although an eighth test was originally included in the battery, it was still undergoing methodological changes during the validation work by Jones and colleagues (2016) when the current study was being initiated and therefore was not included in the current study. During DalCAB development, tasks were chosen to reflect the three attentional networks identified by Posner and Petersen (1990): vigilance, orienting, and executive control (Jones et al., 2015). A computer mouse is used for participants to provide responses. Prior to each task, participants complete practice trials of that task. During the practice trials only, participants

receive auditory feedback indicating whether their responses are correct or incorrect on each trial. The DalCAB instructs participants that they are allowed repeat the block of practice trials, if they so choose.

See below for descriptions of each task. All tasks use playing cards or card suits as stimuli[1]. These task stimuli are used to reduce variation in performance attributable to language abilities when completing the tasks.

Simple Reaction Time (RT) Task.

Stimuli are presented one at a time and participants are required to press the computer mouse as quickly as possibly each time a stimulus is presented. The subsequent stimulus appears according to one of three different response-stimulus intervals between 500 and 1500ms.

Go-No-Go Task.

Stimuli are presented one at a time. Participants are required to respond only to a single target color (i.e., a “go” response) and do nothing otherwise (i.e., a “no” response). The proportion of “go” trials varies from blocks of 80% “go” to 20% “go” during the task.

Choice Reaction Time (RT) Task.

Stimuli are presented one at a time. Participants are required to make a button-press response indicating the color of the stimulus. There are two

color options.

[1] Some details of the DalCAB tasks are deliberately left vague in order to protect the intellectual property of the DalCAB.

Dual Task.

Stimuli are presented one at a time in sets of eight or 12. Participants complete the Choice RT Task while being asked to also count the number of items of each color presented. At the end of each set, a probe for one color appears and participants indicate the number of stimuli of that color that were presented.

Vertical Flanker Task.

Stimuli are presented in a vertical column and participants are asked to make a response indicating the shape of the central target. The central target is either congruent or incongruent with the additional targets flanked on either side.

Item Memory Task.

Stimuli are presented in memory sets of two to six cards. Participants are asked to respond indicating whether a subsequent probe card was present or absent from the memory set.

Visual Search Task.

Participants are to locate a target and respond indicating its orientation. The target is included among six to 18 distractor shapes, depending on the trial. Distractors are either a different color or the same color as the target, resulting in either a feature search or conjunction search, respectively.

For a detailed comparison of how the DalCAB differs from the ANT/ANT-I, the only other existing computerized cognitive assessment measure based on Posner and Petersen's (1990) three attention networks, see Table 5 below.

Table 5. Comparing the Attention Network Test and Dalhousie Computerized Attention Battery.

Test Battery	*Attention Networks*			Overall
	Executive Control	**Vigilance/ alerting**	**Orienting**	
Attention Network Test (ANT)* and Attention Network Test – Interactions (ANT–I)~	Congruency effect: RT difference between responding to targets surrounded by congruent or incongruent flankers.	Referred to as "alerting". RT difference on flanker task trials that are preceded by a warning cue (ANT = visual, ANT-I = auditory) or no cue.	RT difference on the flanker task between having a spatial cue to the target location or only a centre cue (that does not provide predictive spatial information).	Response on the flanker task that are manipulated by exogenous cues. Accuracy can also be calculated for each network.
Dalhousie Computerized Attention Battery (DalCAB)	Includes aspects of four different attention tasks (Item Memory, Go-No-Go, Choice RT, and Dual Tasks) in addition to the Flanker Task.	Referred to as "vigilance". No cues provided, looks at maintaining an alert *state* over time and consistency in responding across five attention tasks (Simple RT, Go-No-Go, Choice RT, Dual, and Visual Search Tasks).	No cues provided, looks at ability to search for visual targets and engage/disengage attention in two attention tasks (Visual Search and Go-No-Go Tasks).	Responses on multiple tasks without cues.

Note. *Fan and colleagues (2002); ~Callejas and colleagues (2005).

2.3 Procedure

Study procedures were reviewed and approved by the Nova Scotia Health Authority Research Ethics Board prior to study recruitment. Participants completed

the study procedures during a single session at the Dalhousie MS Research Unit which took up to two and a half hours. During this study visit, participants were invited to participate in the optional MRI sub-study, which would require a second visit. The Method of this MRI sub-study is described in *Chapter 6*.

During this study visit, participants completed the six standardized paper-and-pencil neuropsychological tests: SDMT, CVLT-II, BVMT-R, COWAT, LNS, and WTAR. Interspersed among these neuropsychological tests were the four self-report questionnaires: FIS, HADS, MOS-PES, and HUI. If participants in the MS group had recently completed (within the past two-weeks) the HUI or SDMT during a clinical visit to the Dalhousie MS Research Unit, those questionnaires were not re-administered and their responses/scores from their prior clinic visit were used for the study. Neuropsychological tests and questionnaires were followed by a brief break, the length of which was determined by the participant. Following this break, the DalCAB was completed. The DalCAB was administered on a Macbook Pro laptop (2.4 GHz Intel Core i7; 8GB of memory) with a 15” screen using a gaming mouse (Microsoft Comfort Mouse 4500).

Although participant demographic characteristics for the MS group were obtained from the Dalhousie MS Research Unit clinical database, the control group completed a questionnaire during their study visit to collect their demographic information. Medical comorbidities in the MS group were obtained from the Dalhousie MS Research Unit clinical database. The control group completed the same medical comorbidities questionnaire that is used as standard of care in the Dalhousie MS Research Unit.

Chapter 3. Assessing Networks of Attention in Multiple Sclerosis and Validating the Dalhousie Computerized Attention Battery

3.1 Background

Cognitive impairments are recognized as a common feature of persons living with MS (Chiaravalloti & DeLuca, 2008) and are associated with a number of negative outcomes, such as loss of employment (Benedict et al., 2005), decreased social integration in their community (Hughes et al., 2015), and worse health-related quality of life (Shawaryn et al., 2002). For persons receiving their initial MS diagnosis, cognitive deficits may be the most functionally limiting impairment. This is becoming increasingly so, as new disease modifying drugs for MS are reducing clinical relapse rates and increasing the time it takes to progress to physical disability milestones (Costello & Kalb, 2019), such as reaching an EDSS of 6.0 (i.e., requiring unilateral constant assistance to walk, such as a cane). The EDSS, the most commonly used and widely recognized method of rating neurological disability (Meyer-Moock et al., 2014), is disproportionately focused on motor symptoms and individuals classified as having low neurologic disability may have significant cognitive impairments that are functionally limiting. Proper assessment and monitoring of cognitive impairments are necessary if treatments targeting cognitive functioning in MS are to be developed and evaluated.

Reported prevalences of cognitive deficits in MS vary widely within each cognitive domain (Grzegorski & Losy, 2017). This is partly due to variability in cognitive function between subtypes of MS (Ruano et al., 2017), but also due to variation in how cognitive domains are assessed and conceptualized. Attention is

a multi-faceted and fundamental cognitive function. It interacts with other cognitive abilities, such as working memory in particular (Knudsen, 2007). Slowed information processing speed is cited as the primary cognitive change in MS, however, cognitive tests used to assess processing speed, memory, and other cognitive domains also require attentional abilities. For example, the Symbol Digit Modalities Test (SDMT), a test consistently recommended for the assessment of processing speed in MS, has been described as a test of both processing speed and attention (Amato et al., 2010; Reuter et al., 2011; A Ruet et al., 2013). Discrepancies in how aspects of attention are conceptualized and described creates barriers in building a body of literature on attentional abilities in MS.

Posner and Petersen (1990) developed a three network model of attention that has stood the test of time in the decades that have followed. The three networks included in the original model are: (1) orienting – the ability to prioritize sensory information by shifting attentional focus, for example, attending to a location in physical space or only one modality, (2) vigilance – establishing and maintaining an alert state in which the individual is *prepared* to detect and response to a stimulus, and (3) executive control – focal or conscious control of attention, including detecting and acknowledging a target, managing conflicting responses, and regulating attentional processes. Each of the networks corresponds to anatomically unique systems (Petersen & Posner, 2012): (1) orienting – appears to function largely within the parietal cortex with connections to frontal areas such as the frontal eye fields and ventral frontal cortex, (2) vigilance – appears to rely on brain stem arousal, such as norepinephrine release from the

locus coeruleus, and systems within the right cerebral cortex, (3) executive control – appears to operate within the lateral frontal and parietal regions (the frontoparietal component of the network), and the medial frontal/cingulate cortex and anterior insula (the cinguloopercular component of the network).

The DalCAB is a novel computerized measure composed of seven tasks of attention, selected due to their existing validation for assessing attention. Initial validation work has shown the DalCAB to map onto the three attention networks described by Posner and Petersen (Jones et al., 2015). The DalCAB produces multiple scores related to each network of attention, capturing subtle differences in attentional abilities within the same network. In addition, baseline RT is assessed and can be used to account for motor speed in subsequent analyses, which was a limitation of previous computerized tests based on Posner and Petersen's model. This is particularly important when assessing persons with MS. Although the DalCAB has been used to assess attentional abilities in other neurologic conditions, such as Parkinson's disease (Drake, 2019), no studies have been conducted with the DalCAB and persons with MS.

The aims of the analyses described in this chapter were to (1) examine whether networks of attention are affected in persons with MS otherwise thought to have low neurologic disability based on their EDSS and (2) examine known groups validity, ecological validity, and concurrent validity [as defined by Wojcik and colleagues (2019)] of a novel computerized measure of attention, the DalCAB, in an MS population. To address aim (1), the data were cleaned (*3.2.2. Data Cleaning*) and attention network performance on the DalCAB was compared

between MS participants and a healthy control group (*3.2.4 Differences in Attention Network Performance Between Groups – Known Groups Validity*). These comparisons between MS participants and controls also provided "known groups" validity identified in aim (2). For completeness, descriptive statistics were run on all DalCAB measures (*3.2.3 Descriptive Statistics*). Before further addressing aim (2), the DalCAB measures relevant to these analyses were selected (*3.2.5. Selection of DalCAB Variables*) and slowed RT in MS was accounted for (*3.2.6 Accounting for Slowed Reaction Times in MS on the DalCAB*). Consistent with aim (2), associations between the DalCAB and commonly examined clinical characteristics, such as EDSS and health-related quality of life, were explored to provide ecological validity (*3.2.7 DalCAB Correlations with Clinical Characteristics – Ecological Validity*). Then, associations between the DalCAB and standard neuropsychological tests were calculated to provide concurrent validity (*3.2.8 DalCAB Compared to Neuropsychological Tests – Data Preparation* and *3.2.9 DalCAB and Standard Neuropsychological Tests – Concurrent Validity*). For completeness, MS and control participant's performance on the standard neuropsychological tests was compared (*3.2.10 Standard Neuropsychological Tests – Performance Between Groups*).

We hypothesized that attention networks would differ between persons with MS and control participants. The nature of these differences was uncertain given the inconsistency in previous literature on attention network performance in MS and this being the first use of this computerized measure, the DalCAB, in an MS population. We also hypothesized that the DalCAB would demonstrate the

appropriate types of validity in this population, given existing work validating it in healthy populations and previous use in populations such as Parkinson's Disease and patients who require general anesthesia.

3.2 Data Analyses and Results

3.2.1 General Notes

To control for type I error rate due to multiple comparisons a Benjamini-Hochberg correction was used throughout the current study analyses. This method allows for additional power compared to more conservative methods such as the Bonferroni correction (Benjamini & Hochberg, 1995). All data analyses for the current study were conducted with SPSS Statistics version 25.0.

3.2.2 Data Cleaning

For DalCAB tasks, only trials with correct responses were used in the RT analyses. The DalCAB imposes cut-off time limits in which participants must respond (i.e., maximum response times). Maximum response times increase as task demands increase, so to allow ample time for the individual to respond. RTs less than 100ms were excluded from analyses as they were considered anticipatory responses (e.g., beginning to respond before the stimulus was perceived). No additional steps were taken to remove "extreme values" during data analyses. This approach is consistent with the conclusions of Ulrich and Miller (1994), as well as Baayen and Milin (2010), who examined the bias associated with various methods of cleaning RT datasets. These authors concluded that significant bias is introduced by a-priori data trimming and truncating data sets (e.g., excluding values two SD above the mean). A-priori data trimming and

truncating data sets are likely to minimize effects in RT data, which is typically skewed. Validation work on the DalCAB by Jones and colleagues (2016) reported the average skewness across tasks to be 2.24 (range: 1.53-3.15), which indicates the RT data from the DalCAB are right-skewed, as expected.

3.2.3 Descriptive Statistics

During the validation of the DalCAB in young healthy adults (aged 18 to 31), Jones and colleagues (2015) conducted a factor analysis on their 7 computerized tasks. The final model included 22 variables. These variables were hypothesized to represent different aspects of attention and were grouped into Posner and Petersen's (1990) three networks of attention: orienting, vigilance, and executive control. These 7 tasks were collected in the current study and the same 22 variables were used in the current analyses. Although other DalCAB variables could have been included in the current analyses, only these 22 variables were selected given the existing work dividing these variables by attention networks. Descriptive statistics for all 22 DalCAB variables are provided in Table 6.

The following DalCAB participant data are missing: One control participant did not complete the Visual Search Task, four MS participants did not complete the Dual Task correctly and their data were removed, and one control participant did not have enough correct trials to calculate the Simple RT Task – response stimulus interval effect. Measures where this is applicable are noted in Table 6. All missing data in the current thesis are listed in Supplementary Table 1. All DalCAB measures are described in Supplementary Table 2.

Table 6. Descriptive Statistics for DalCAB Measures.

Associated Network of Attention	DalCAB Measures	MS Group (*n* = 104)	Control Group (*n* = 40)
	Mean SRT	313.8 (86.0)	266.5 (42.2)
Vigilance	VS Feature search mean RT*	789.1 (135.7)	706.0 (88.8)
	VS Feature search set size effect (RT)*	1.6 (7.4)	1.8 (5.2)
	CRT-SRT Decision speed (RT)	177.6 (95.0)	166.5 (50.2)
	SRT response stimulus interval effect (RT)*	43.8 (59.2)	44.1 (44.3)
	GNG 20% vigilance decrement (RT)	2.0 (12.6)	1.1 (1.7)
	DT switch-cost (RT)	154.1 (80.5)	101.6 (72.3)
	CRT standard deviation	124.4 (40.0)	95.9 (27.3)
	SRT standard deviation	74.7 (34.9)	62.4 (25.0)
Orienting	GNG proportion effect (RT)	-21.7 (40.3)	-27.1 (32.9)
	VS Conjunction search mean RT*	1765.9 (403.4)	1528.7 (242.8)
	VS Conjunction search set size effect (RT)*	79.6 (34.5)	60.8 (26.0)
Executive Control	GNG 20% go percent false alarm	.005 (.01)	.01 (.01)
	GNG 80% go percent false alarm	.01 (.02)	.01 (.01)
	GNG 80% vigilance decrement (RT)	-.6 (1.3)	-.3 (0.7)
	IM mean RT	1201.6 (238.2)	1058.7 (217.3)
	IM set size effect (RT)	74.7 (62.0)	65.4 (52.9)
	IM set size effect (accuracy)	.04 (.04)	.04 (.04)
	IM target absent effect (RT)	1232.7 (302.4)	1073.6 (239.5)
	VF congruency effect (accuracy)	.7 (6.7)	.02 (.05)

Associated Network of Attention	DalCAB Measures	MS Group (*n* = 104)	Control Group (*n* = 40)
Executive Control	CRT switch-cost (accuracy)	.006 (0.04)	.003 (.04)
	DT cost (RT)~	708.0 (141.6)	602.6 (105.5)

Note: Values are Mean (SD); RT = Reaction time, reported in milliseconds; **N* = 143; ~*N* = 140; Variable names listed here are consistent with Jones and colleagues (2015): SRT = Simple Reaction Time, CRT = Choice Reaction Time, DT = Dual Task, GNG = Go-No-Go, IM = Item Memory (also referred to in other literature as the Sternberg Task), VF = Vertical Flanker, VS = Visual Search.

3.2.4 Differences in Attention Network Performance Between Groups – Known Groups Validity

As people living with MS are known to have slower RT, it was important to account for variability in DalCAB performance between the MS and control groups due to differences in baseline RT alone (i.e., slowed motor speed in MS). To do so, Simple RT Task – Mean RT was used to represent baseline RT and was included as a covariate when comparing attention network performance between the MS and control groups. Simple RT Task – Mean RT differed between MS and control groups, as expected, using an independent samples t-test equal variances not assumed [$t(133.9) = 4.4$, $p < 0.001$]. Although Simple RT Task – Mean RT loaded onto the factor associated with the vigilance network in the Jones and colleagues (2015) factor analysis, in the current study this outcome measure is only used to represent baseline RT. Reicker, Tombaugh, Walker, and Freedman (2007) also used a similar "simple RT" task to represent baseline RT in their work on cognition in MS.

Twenty-one Analyses of Covariance (ANCOVA) were run, one for each of the remaining DalCAB measures. Each ANCOVA included group membership

(MS vs control) as the independent measure and Simple RT Task – Mean RT as a covariate. As such, each ANCOVA model examined whether the DalCAB measure differed between the MS and control groups when controlling for variance in baseline RT.

All ANCOVA results are listed in Table 7. All shaded cells in Table 7 indicate a significant difference between groups after accounting for baseline RT. For all measures using RT, the MS group was significantly slower than the control group, however, for Go-No-Go Task – 20% Go Percent False Alarm (a measure of accuracy) the MS group had fewer false alarms than the control group. Of the 8 DalCAB outcomes associated with the vigilance network, 3 differed between the MS and control groups. Of the 3 DalCAB outcomes associated with the orienting network, 2 differed between the MS and control groups. Of the 10 DalCAB outcomes associated with the executive control network, 4 differed between the MS and control groups.

In addition, Table 7 reports whether the covariate of baseline RT (i.e., Simple RT Task – Mean RT) explained significant variance in the DalCAB measure of interest. A significant f-test indicates that baseline RT did explain significant variance in the DalCAB measure. This is not an issue for the between group comparisons given that, as stated above, the variance due to baseline RT is already accounted for in the comparisons.

Table 7. Differences in Attention Network Performance Between MS and Control Groups.

Network of Attention	DalCAB Measures	Does the MS group differ from control?	Effect Size	*Contribution of covariate
Vigilance	VS Feature search mean RT	$F(1,140) = 4.698$, $p = .032$	.032	$F(1,140) = 45.376$, $p < .001$
	VS Feature search set size effect (RT)	$F(1,140) = .027$, $p = .870$		$F(1,140) = .022$, $p = .883$
	CRT-SRT Decision speed (RT)	$F(1,141) = 2.350$, $p = .128$		$F(1,141) = 9.745$, $p = .002$
	SRT response stimulus interval effect (RT)	$F(1,140) = .175$, $p = .676$		$F(1,140) = 2.206$, $p = .140$
	GNG 20% vigilance decrement (RT)	$F(1,141) = .156$, $p = .693$		$F(1,141) = .048$, $p = .827$
	DT switch-cost (RT)	$F(1,140) = 8.653$, $p = .004$	.059	$F(1,140) = 3.754$, $p = .055$
	CRT standard deviation	$F(1,141) = 7.176$, $p = .008$	.048	$F(1,141) = 58.696$, $p < .001$
	SRT standard deviation	$F(1,141) = .990$, $p = .321$		$F(1,141) = 254.384$, $p < .001$
Orienting	GNG proportion effect (RT)	$F(1,141) = 2.463$, $p = .119$		$F(1,141) = 9.253$, $p = .003$
	VS Conjunction search mean RT	$F(1,140) = 4.850$, $p = .029$	.033	$F(1,140) = 31.149$, $p < .001$
	VS Conjunction search set size effect (RT)	$F(1,140) = 5.896$, $p = .016$	.040	$F(1,140) = 4.834$, $p = .030$

Network of Attention	DalCAB Measures	Does the MS group differ from control?	Effect Size	Contribution of covariate*
Executive Control	GNG 20% go percent false alarm	$F(1,141) = 4.377$, $p = .038$	.030	$F(1,141) = 2.666$, $p = .105$
	GNG 80% go percent false alarm	$F(1,141) = 1.380$, $p = .242$		$F(1,141) = .559$, $p = .456$
	GNG 80% vigilance decrement (RT)	$F(1,141) = 3.699$, $p = .056$		$F(1,141) = .803$, $p = .372$
	IM mean RT	$F(1,141) = 6.541$, $p = .012$	.044	$F(1,141) = 6.468$, $p = .012$
	IM set size effect (RT)	$F(1,141) = 3.458$, $p = .065$		$F(1,141) = 14.453$, $p < .001$
	IM set size effect (accuracy)	$F(1,141) = .906$, $p = .343$		$F(1,141) = 3.351$, $p = .069$
	IM target absent effect (RT)	$F(1,141) = 4.842$, $p = .029$	.033	$F(1,141) = 7.578$, $p = .007$
	VF congruency effect (accuracy)	$F(1,141) = .295$, $p = .588$		$F(1,141) = .030$, $p = .863$
	CRT switch-cost (accuracy)	$F(1,141) = 1.147$, $p = .286$		$F(1,141) = 6.193$, $p = .014$
	DT cost (RT)	$F(1,137) = 9.361$, $p = .003$	.064	$F(1,137) = 24.293$, $p < .001$

Note: *Indicates whether the covariate of baseline RT (i.e., Simple RT Task – Mean RT) explained significant variance in the DalCAB measure of interest; Reported effect size is partial eta squared (η^2_p); Effect size is only reported for statistically significant results; DalCAB measures that differ between MS and control are shaded; All 21 statistically significant results remained after Benjamini-Hochberg correction for multiple comparisons.

Partial eta squared (η^2_p) is used as a measure of effect size. The strength of the effect size is interpreted as: small (0.01), medium (0.09), or large (0.25; Cohen, 1992). For list of labels used to describe the magnitude of effect sizes and correlations, see Supplementary Table 3.

3.2.5 Selection of DalCAB Measures

To reduce the number of comparisons, only DalCAB measures shown in Table 7 of the previous section, above, to differ between the MS and control groups were used (9 measures). The 9 selected measures represented each of the three attention networks outlined by Posner and Petersen (1990): vigilance [(1) Visual Search Task Feature Search – Mean RT, (2) Dual Task – Switch-Cost, (3) Choice RT Task – Standard Deviation], orienting [(4) Visual Search Task Conjunction Search – Mean RT, (5) Visual Search Task Conjunction Search – Set Size Effect], and executive control [(6) Go-No-Go Task – 20% Go Percent False Alarm, (7) Item Memory – Mean RT, (8) Item Memory – Target Absent Effect (RT), (9) Dual Task – Cost]. Simple RT Task – Mean RT, used as the covariate in these analyses, is examined in subsequent analyses where appropriate such that the remaining analyses include a total of 10 DalCAB measures of interest.

3.2.6 Accounting for Slowed Reaction Time in MS on the DalCAB

After determining which DalCAB measures differed between MS and control groups beyond differences in baseline RT, in *Chapter 3.2.4 (Differences in Attention Network Performance Between Groups – Known Groups Validity)*, it was necessary to continue accounting for baseline RT when conducting further analyses with the DalCAB measures. Linear regression was used to parse out variation in DalCAB measures due to baseline RT (Simple RT Task – Mean RT), leaving unstandardized residual DalCAB scores. Unstandardized residual scores were chosen in place of standardized residuals as unstandardized values on the DalCAB represent milliseconds – an easily interpreted unit of measurement. These

residuals were used for all subsequent analyses described below. As an exception, the Go-No-Go Task – 20% Go Percent False Alarm measure was used without removing variation due to baseline RT, as it is a measure based on accuracy not speed.

Unless otherwise specified, no steps were taken to account for variation in standard neuropsychological test scores that may be accounted for by baseline RT differences between groups. This approach was chosen as standard neuropsychological tests are typically used in clinical settings without the addition of computerized measures. Thus, removing the variation due to the Simple RT Task – Mean RT in the standard neuropsychological test scores would not have allowed for comparisons with previously published literature using these tests. In addition, removing this variation would have limited the comparisons of the DalCAB and standard neuropsychological tests data from the standpoint of establishing ecological validity of the DalCAB. By contrast, as the DalCAB is an experimental measure and contains seven tasks, it was important to determine whether any utility of the DalCAB lies solely in the Simple RT Task, or if the remaining six tasks also provided unique and valuable information.

3.2.7 DalCAB Correlations with Clinical Characteristics – Ecological Validity

Spearman non-parametric correlations (two-tailed) were used to explore associations between attention network performance, demographics (age, years of education – MS and control), health-related quality of life (single attribute utility score on the HUI), and clinical characteristics (EDSS, years since onset – MS

group only). As years since onset and years since diagnosis were highly correlated (r_s = 0.945, p < 0.001), only years since MS onset was included in the analyses.

See Table 8 for all correlations. In the MS group, EDSS was significantly correlated with measures in the vigilance network, as well as the Simple RT Task – Mean RT. Years since MS onset was correlated with measures all three attention networks, but not the Simple RT Task – Mean RT. In the combined MS and control group, age was correlated with DalCAB measures from all three attention networks, however, years of education was correlated only with 2 of the 10 measures. Health-related quality of life on the HUI was correlated with measures from the vigilance and orienting networks as well as the Simple RT Task – Mean RT.

In order to gain further information on the health-related quality of life in this sample for comparison to previous literature, an additional comparison was made between the HUI single attribute utility score and EDSS. Health-related quality of life on the HUI was correlated with EDSS (r_s = -0.429, p <0.001). The MS group endorsed significantly lower health-related quality of life on the HUI compared to the control group [t(140.8) = -6.9, p < 0.001]. Age and years of education were previously compared between groups (See *Chapter 2.1 Control Group*, above).

Table 8. Correlations between DalCAB Measures and Participant Characteristics.

DalCAB Measures *(Across)* / **Participant Characteristics** *(Below)*	Simple RT	Vigilance Network			Orienting Network		Executive Control Network			
		VS Feature search mean RT	DT switch-cost	CRT standard deviation	VS Conjunction search set size effect	VS Conjunction search mean RT	GNG 20% go percent false alarm	IM mean RT	IM target absent effect RT	DT cost
MS group only										
EDSS	.316	.200	.093	.213	.073	.125	.138	.135	.004	.049
Years since MS onset	.096	.170	.200	.041	.290	.283	.066	.012	.031	.309
MS and Control										
Age	.306	.287	.219	.123	.279	.236	.033	.135	.119	.178
Years of education	-.153	-.140	-.234	-.099	-.064	-.109	-.014	-.014	-.018	-.178
HRQoL	-.205	-.231	-.121	-.303	-.127	-.229	-.075	-.142	-.081	-.079

Note. HRQoL = Health-related quality of life, represented by the HUI single attribute utility score; DalCAB measures relating to the attention networks have the variance attributed to Simple RT Task – Mean RT parceled out; Shaded cells represent significant Spearman non-parametric correlations (two-tailed); All 19 significant correlations were jointly subjected to a Benjamini-Hochberg correction and remained significant.

None of the significant correlations reported in Table 8, above, exceed a strength of "weak" (0.1 – 0.3). The strength of correlations throughout this thesis were interpreted based on the following scale, recommended for use in psychology: 0.1 – 0.3 = weak; 0.4 – 0.6 = moderate; 0.7 – 0.9 = strong; 1.0 = perfect (Dancey & Reidy, 2007). For list of labels used to describe the magnitude of correlations and effect sizes, see Supplementary Table 3.

3.2.8 DalCAB Compared to Neuropsychological Tests – Data Preparation

Standard Neuropsychological Tests – Normative Values

Raw scores on most neuropsychological tests were converted to z-scores using Canadian regression-based norms adjusted for age, sex, and years of education (Walker et al., 2017): SDMT Total, CVLT-II Total Immediate Recall, BVMT-R Total Immediate Recall, COWAT Phonemic Total, and COWAT Semantic Total. The norms by Walker and colleagues (2017) are based on 330 healthy adults from 3 Canadian cities. For tests where Canadian norms were not available, raw scores were converted based on American normative data controlling for age [LNS Total: The Psychological Corporation (1997); BVMT-R Long Delay Free Recall: Benedict (1997)], both age and sex [remaining CVLT-II scores: Delis and colleagues (2000)], or both age and years of education [WTAR Total: Wechsler (2001)].

Standard Neuropsychological Tests – Cut-off Score for Impairment

Participants were classified as "impaired" on neuropsychological tests using a cut-off of $z \leq -1.5$. Cut-offs for cognitive impairment in MS literature are commonly

1.5 or 2.0 SD below the mean [see Table 1. Cognitive Impairment (CI) in Early MS Disease Course from *Chapter 1.5 (Cognition in MS)* for examples]. In a previous study comparing 59 persons with MS and 152 controls, a $z \leq -1.0$ was shown to classify the majority of healthy control participants as cognitively impaired, in addition to the persons with MS (Sepulcre et al., 2006). The proportion of MS participants classified as cognitively impaired was similar using a cut-off of -1.5 and -2.0 (77.96% and 66.10%, respectively). In the current study, a cut-point of -1.5 SD was selected, over -2.0 SD, as it is also consistent with the two lowest ranges of classifying cognitive performance on the Wechsler Adult Intelligence Scale – Fourth Edition (i.e., "Very Low Range" and "Extremely Low Range"), a widely used and validated standard neuropsychological test battery (Wechsler, 2008). Note that participants were classified as "impaired" on the COWAT if they had a $z \leq -1.5$ on either their Phonemic Total or Semantic Total (referred to as COWAT Total).

3.2.9 DalCAB and Standard Neuropsychological Tests – Concurrent Validity

In order to examine the concurrent validity of the DalCAB in an MS population, comparisons between the DalCAB and standard neuropsychological test scores were conducted. Spearman non-parametric correlations (two-tailed) were used to explore associations between DalCAB measures and the standard neuropsychological test scores in the entire sample (MS and control groups).

Correlations between the standard neuropsychological test scores and DalCAB measures are shown in Table 9. The Simple RT Task – Mean RT was

correlated with all standard neuropsychological test scores, except CVLT-II Trial 1. SDMT Total was correlated with measures across all three attention networks. All CVLT-II scores were associated with the vigilance network, except for CVLT-II Trial 1 which was not associated with any attention network measures. BVMT-R Total Immediate Recall and Long Delay Free Recall were both associated with the orienting network. Only the BVMT-R Total Immediate Recall was associated with the executive control network and only the BVMT-R Long Delay Recall was associated with the vigilance network. COWAT Semantic Total was associated with the orienting and executive control networks, however, COWAT Phonemic Total was not associated with any attention network measures.

Table 9. Correlations between DalCAB Measures and Neuropsychological Tests in MS and Control Participants.

DalCAB Measures *(Across)* / **Neuropsychological Test Scores** *(Below)*	Simple RT	Vigilance Network			Orienting Network		Executive Control Network			
		VS Feature search mean RT	DT switch-cost	CRT standard deviation	VS Conjunction search mean RT	VS Conjunction search set size effect	GNG 20% go percent false alarm	IM mean RT	IM target absent effect RT	DT cost
SDMT										
Total	-.502	-.333	-.037	-.283	-.259	-.151	.074	-.193	-.169	-.086
CVLT-II										
Trial 1	-.154	-.107	.025	-.043	-.026	-.014	.145	-.012	-.070	-.061
Total Immediate Recall	-.298	-.144	-.094	-.288	-.070	-.035	.024	-.032	-.089	-.082
SD Free Recall	-.286	-.141	-.096	-.257	-.117	-.037	.029	.003	-.077	-.129
SD Cued Recall	-.253	-.099	-.088	-.207	-.077	-.006	.108	-.014	-.066	-.026
LD Free Recall	-.300	-.111	-.080	-.196	-.091	-.036	.070	-.011	-.044	-.082
LD Cued Recall	-.263	-.104	-.021	-.208	-.102	-.055	.013	-.009	-.058	-.010
BVMT-R										
Total Immediate Recall	-.253	-.095	.051	-.123	-.211	-.167	-.017	-.189	-.205	.043
Long Delay Free Recall	-.239	-.174	.024	-.093	-.184	-.113	.103	-.148	-.159	.003
COWAT										
Phonemic Total	-.192	-.059	-.135	-.063	-.055	-.073	.141	.016	.019	-.052
Semantic Total	-.403	-.134	-.056	-.122	-.157	-.177	.204	-.170	-.163	-.059

Note. Spearman non-parametric correlations; In this table SD = Short Delay, LD = Long Delay; DalCAB measures relating to the attention networks have the variance attributed to Simple RT Task – Mean RT parceled out; Significant values are shaded; All values remained significant after Benjamini-Hochberg correction for multiple comparisons.

To demonstrate that the correlations between the standard neuropsychological test scores and DalCAB measures cannot be accounted for solely by the association with the Simple RT Task – Mean RT, linear regression was used to parse out variation in neuropsychological test scores accounted for by Simple RT Task – Mean RT (i.e., as was done for the DalCAB measures). These residuals were then used for examining the correlations between neuropsychological test scores and attention network performance. No changes were observed with regards to which tests were associated with which attention networks, except that BVMT-R Long Delay Free Recall was no longer associated with the vigilance network (data not shown).

3.2.10 Standard Neuropsychological Tests – Performance Between Groups

To allow comparisons between the current analyses and MS sample to previous literature, participants were also compared on their performance on the standard neuropsychological tests. These analyses were conducted for completeness, in order to quantify cognitive performance in the MS sample. They were not intended to fulfill an aim of this chapter.

Independent samples t-tests (equal variances not assumed) were used to determine whether the MS group differed from the control group in their performance on the standard neuropsychological tests (z-scores and t-scores). Pearson chi-square tests were used to compare whether the proportion of participants classified as “impaired” on neuropsychological tests differed between the MS and control groups.

The MS group had significantly lower performance on all scores of interest across the standard neuropsychological tests, with the exception of BVMT-R Total Immediate Recall. Descriptive values for neuropsychological test scores and p-values for all group comparisons are reported in Table 10.

Table 10. Descriptive Statistics and Comparisons between MS and Control Groups for the Standard Neuropsychological Tests.

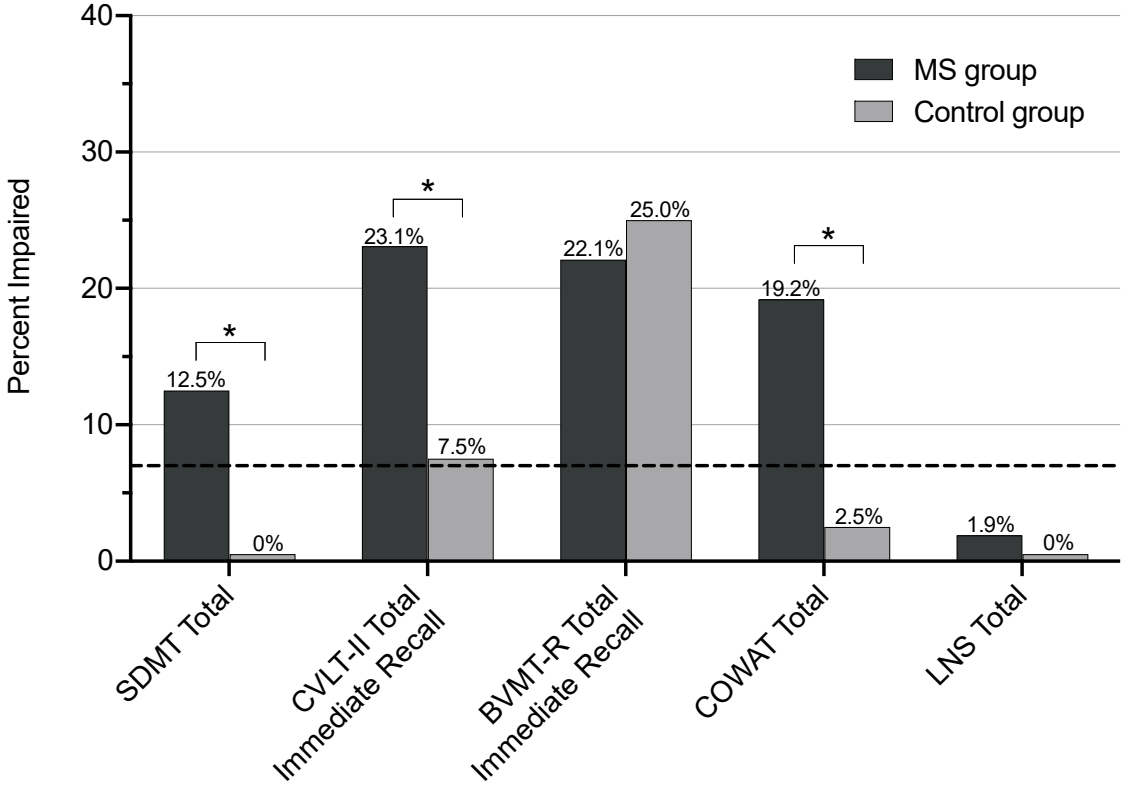
Neuropsychological Test Scores	**MS Group**	**Control Group**	**Effect Size**	**P-value**
SDMT				
Total~	-.202 (1.300)	.442 (0.817)	.54	.001
CVLT-II				
Trial 1	-.476 (1.039)	.175 (0.836)	.66	<.001
Total Immediate Recall	-.773 (1.192)	-.043 (0.894)	.66	<.001
Short Delay Free Recall	-.238 (1.092)	.412 (0.854)	.63	<.001
Short Delay Cued Recall	-.250 (1.073)	.413 (0.823)	.66	<.001
Long Delay Free Recall	-.269 (1.130)	.400 (0.826)	.64	<.001
Long Delay Cued Recall	-.216 (1.083)	.350 (0.681)	.58	<.001
BVMT-R				
Total Immediate Recall	-.618 (1.250)	-.289 (1.363)	.26	.189
Long Delay Free Recall*	48.190 (13.151)	53.980 (12.407)	.44	.016
COWAT				
Phonemic Total	.282 (1.140)	1.173 (1.035)	.80	<.001
Semantic Total	-.477 (1.089)	.093 (0.888)	.55	.002
LNS				
Total	.199 (0.888)	.542 (0.798)	.80	.028
WTAR				
Total	.563 (0.747)	.896 (0.808)	.44	.027

Note. Mean (SD); The majority of values are z-scores. *Denotes t-scores; P-values from independent samples t-test, equal variances not assumed; ~One control participant did not complete the SDMT correctly and their data is excluded; Shaded cells remained significant after Benjamini-Hochberg correction for multiple

comparisons. Effect sizes are Cohen's D, calculated using Lakens (2013) effect size calculator.

Prevalence of impairment varied across domains assessed (See Figure 3). Based on the normal distribution, approximately 7% of the population would be expected to fall 1.5 SD below the mean. The MS group had a higher prevalence of impairment than would be expected in the general population on all tests except LNS Total. As only one person in the MS group met the criteria for impairment on LNS Total and none in the control group, this test was excluded from the remaining analyses in this thesis. For BVMT-R Total Immediate Recall, 10 participants in the control group (25%) met criteria for impairment on this test. As this was unexpected, impairment rates were also calculated based on the available American norms (normative values control for age; Benedict, 1997) rather than the Canadian norms described above; The same 10 participants continued to meet criteria for impairment.

Figure 3. Prevalence of Impairment on Neuropsychological Tests.



Note. *Indicates the proportion of individuals impaired in the MS and control groups is significantly different at $p < 0.05$, using Pearson Chi-Squared test; Proportion of individuals that could be expected to fall 1.5 SD below the mean based on a normal distribution is represented by the dotted line.

As the WTAR Total differed between groups, this could represent a limitation of the current analyses as it is possible that our sample of persons with MS had lower cognitive functioning than our control group prior to the onset of their MS. The WTAR is considered a method of estimating an individual's premorbid level of cognitive functioning (i.e., functioning prior to the onset of injury or disease). It has been shown to be relatively robust to malingering (Whitney, Shepard, Mariner, Mossbarger, & Herman, 2010) and remains stable as other cognitive functions improve post-brain-injury (R. E. Green et al., 2008). In order to demonstrate that significant between group differences on the WTAR Total did not

account for the differences in cognitive performance between the MS and control groups, and therefore were not problematic for interpreting the remaining analyses in the current thesis, all standard neuropsychological test scores (except LNS Total) were again compared between groups with the variation due to WTAR Total regressed out. All previous between group differences remained (data not shown) except for BVMT-R Long Delay Free Recall, which was no longer significant between groups [$t(71.34) = 1.95$, $p = 0.055$].

Although Simple RT Task – Mean RT was not accounted for when conducting analyses using the standard neuropsychological tests, to maintain the ecological validity of these test scores, the relationship between Simple RT Task – Mean RT and the neuropsychological test scores was still examined. All neuropsychological test scores (except LNS Total) were again compared between the MS and control group, this time with the variation due to Simple RT Task – Mean RT regressed out. In these analyses, the SDMT Total no longer significantly differed between groups [$t(39.00) = 1.01$, $p = 0.319$], the BVMT-R Long Delay Free Recall no longer differed between groups [$t(69.98) = 1.92$, $p = 0.237$], and the COWAT Semantic Total no longer differed between groups [$t(79.41) = 1.92$, $p = 0.058$]. The other statistically significant differences between groups remained.

3.3 Discussion

The analyses described in the current chapter (1) examined whether networks of attention were affected in persons with MS otherwise thought to have low neurologic disability based on their Extended Disability Status Scale (EDSS)

and (2) sought to validate a novel computerized measure of attention, the Dalhousie Computerized Attention Battery (DalCAB), in an MS population.

Persons with MS differed from age, level of education, and gender matched control participants in their performance on DalCAB measures reflecting all three attention networks: executive control, orienting, and vigilance [also referred to as "alerting" on the Attention Network Test (ANT)]. This was the case after accounting for baseline reaction time (RT) differences between the MS and control participants. The current results differ from previous work examining Posner and Peterson's (1990) three attention networks in persons with MS that have used the ANT – the only other computerized measure used in MS designed to assess these attention networks. Previous studies using the ANT found that only the vigilance/alerting network differed between MS and controls groups (Urbanek et al., 2010), including in an MS sample with relatively mild neurologic disability (Crivelli et al., 2012). However, despite both of these studies attempting to account for the equivalent of "baseline RT", their "baseline RT" measures were taken from tasks that required decision making in addition to a simple motor response (e.g., deciding whether an arrow was pointing left or right).

By contrast, when using the ANT-Interactions (ANT-I), only the executive control network was found to differ between MS and control groups (Wojtowicz et al., 2013) and no differences between networks were found in other studies (Ishigami et al., 2013; Omisade et al., 2012). These studies did not control for baseline RT differences between groups. Despite these differences, all five studies identified similar interactions. Persons with MS benefitted less from warning

signals (i.e., used to assess the vigilance/alerting network on the ANT) when the subsequent target was accompanied by an incongruent flanker (i.e., used to assess the executive control network). This did not occur in the control group, who were found to benefit from the warning signal whether or not the subsequent target was accompanied by an incongruent flanker. However, the modality in which "warning signals" were provided varied between studies, with Urbanek and colleagues (2010) and Crivelli and colleagues (2012) providing visual warning signals and the remaining three studies using auditory warning signals. This interaction experienced between the vigilance/alerting and executive control networks by the MS samples supports that further distinction between the cognitive processes associated with each attention network is necessary. One global score per network, as is provided with the ANT/ANT-I, does not appear to provide the diversity of information necessary to understand how attention networks are affected in MS. Sumowski and colleagues (2018), who recently identified the key future priorities for the field of cognition in MS, highlighted that future research should consider latent variables "as purer measures of targeted functions" (p. 2). There are key differences between the ANT and the DalCAB with regards to how the attention networks are assessed, in addition to the ANT only providing one score per network as described above. See the previously discussed Table 5 (*Chapter 2.2.4 Experimental Neuropsychological Assessment Measures - Dalhousie Computerized Attention Battery*) for comparisons.

3.3.1 Vigilance Network

Persons with MS differed from the control group on three of the eight measures associated [in the original Jones and colleagues (2015) factor analysis] with the vigilance network, even after accounting for baseline RT differences between groups. Based on the aspects of the vigilance network that differed between groups, this MS sample was: (1) slower at target detection and (2) had more difficulty maintaining consistency in their responses. The MS sample appeared to have intact response preparedness and were equally fast as controls when making decisions requiring a light cognitive load. The MS sample appeared to have intact ability to maintain a prepared state when looking across the entirety of a task, however, consistency in responses across trials was as issue as mentioned above. These differences are discussed more thoroughly, by task, below.

Simple RT Task.

Neither of the Simple RT Task measures associated with the vigilance network differed between MS and control participants: Response Stimulus Interval Effect (RT) and Standard Deviation. In the general population, individuals are faster to respond when there are longer intervals between trials (i.e., response stimulus intervals), which is considered to be associated with implicit temporal preparation (Vallesi, Lozano, & Correa, 2013). As there were no differences between groups for this measure, this indicates that persons with MS and controls benefitted equally from the longer preparation times prior to responding. Similarly, the groups did not differ in Simple RT Task – Standard Deviation. The current study

accounted for differences in baseline RT between groups using Simple RT Task – Mean RT, which may have been too closely related to Simple RT – Standard Deviation for that measure to still differ between groups.

Go-No-Go Task.

The one measure from the Go-No-Go Task associated with the vigilance network, 20% Vigilance Decrement (RT), did not differ between MS and controls. Although the majority of Go-No-Go Task measures are associated with the executive control network (three of the five), the 20% Vigilance Decrement (RT) was categorized into the same factor as the Simple RT Task – Response Stimulus Interval Effect (RT), described above, in the previous DalCAB factor analysis work (Jones et al., 2015). In the previous DalCAB factor analysis, these two measures combined together were thought to represent “preparation and maintenance” (p. 7): ability to be prepared to provide a response and ability to maintain that prepared (i.e., vigilant) state over time. Neither of these processes were affected in the MS group.

Decision Speed.

Choice/Simple RT Task – Decision Speed (RT) is calculated using both the Simple RT Task and Choice RT Task, and represents the time it takes a participant to choose between the two response options in the Choice RT Task. This measure did not differ between groups in the current study. Others have also found that decision speed, based on simple RT and choice RT tasks, do not differ between MS and controls (Reicker et al., 2007; Stoquart-ElSankari et al., 2010), with Reicker and colleagues (2007) suggesting that this may reflect that the processing

required to perform a two-response discrimination task represents only a “light cognitive load”.

Choice and Dual RT Tasks.

Both Dual Task – Switch Cost (RT) and Choice RT Task – Standard Deviation did differ between MS and control groups in the current study. In the previous factor analysis of the DalCAB, these two measures were associated with the factor representing “consistency in participant responses” (p. 7, Jones et al., 2015). These results suggest that persons with MS with relatively low neurologic disability, as in the current study, have more difficulty maintaining consistency in their responses compared to controls. This is in keeping with previous work examining response consistency in MS using intra-individual variability (IIV), which found persons with MS to have increased variability compared to controls even when the overall slowed RT of persons with MS was accounted for (Wojtowicz et al., 2012; Wojtowicz et al., 2013).

Visual Search Task.

Of the two Visual Search Task measures associated with the vigilance network, only Feature Search – Mean RT differed between the MS and control groups, whereas the Feature Search – Set Size Effect (RT) did not. In feature search trials, the target is a different color than the distractors and is easily spotted. Feature Search – Mean RT and Feature Search – Set Size Effect (RT) are therefore thought to reflect preparedness to respond and basic target detection (Jones et al., 2015). In the DalCAB, making a two-choice decision regarding the target (i.e., upright or upside down) also occurs. As other measures of response

preparedness [i.e., Simple RT Task – Response Stimulus Interval Effect (RT), above] and decision speed [i.e., Choice/Simple RT Task – Decision Speed (RT), above] did not differ between our MS and control groups, the significant difference in Feature Search – Mean RT more likely represents a discrepancy in target detection between groups. Utz and colleagues (2013) similarly found their sample of 38 persons with RRMS to differ from controls in RT on a feature search task, but the authors did not control for baseline RT differences. Increased RT on feature search is also seen in persons with mild cognitive impairment and Alzheimer's disease, even when differences in overall slowing of RT between groups are accounted for (Tales, Haworth, Nelson, J. Snowden, & Wilcock, 2005). Increased set size (i.e., more distractor stimuli) does not increase RT when healthy adults or even adults with visual impairments conduct a feature search (Kuyk, Liu, & Fuhr, 2005), as the target is easily identified regardless of the number of distractors. Thus, the fact that this measure did not differ between this sample of persons with MS with low neurologic disability and controls in the current study is reasonable.

3.3.2 Executive Control Network

Persons with MS differed from the control group on four of the ten DalCAB measures associated [in the original Jones and colleagues (2015) factor analysis] with the executive control network, even after accounting for baseline RT differences between groups. Based on the aspects of the executive control network that differed between groups, this MS sample: (1) was slower overall at initiating their scan of items held in working memory (i.e., their zero-intercept for scanning time differed from controls), and (2) had more difficulty switching between

responses when attention was divided between two tasks. Yet this MS sample was not affected more than controls by an increased load on their working memory (i.e., their working memory scanning rate did not differ from controls). The MS sample did not exhibit a greater change in their RT over the course of a task, did not exhibit deficits in inhibitory control, did not have more difficulty switching between types of response within a task, and their conflict monitoring appeared to be intact in comparison to the control group. The control group had more false alarms in some instances compared to the MS group, likely due to decreased RT in the control group. These discrepancies suggest that among the two components of the executive control network outlined by Petersen and Posner (2012; frontoparietal and cinguloopercular components), the frontoparietal component responsible for task initiation, setting, and switching appears to be more affected in this sample of persons with MS compared to the cinguloopercular component (related to maintenance and monitoring of errors). These differences are discussed more thoroughly, by task, below.

Item Memory Task.

Of the four measures from the Item Memory Task that were associated with the executive control network, Mean RT and Target Absent Effect (RT) did differ between the groups, yet Set Size Effect (Accuracy) and Set Size Effect (RT) did not. This was the same pattern reported by Janculjak and colleagues (1999), who found that the set size effect (i.e., slower RTs and lower accuracy for larger set sizes; Sternberg, 1969) did not differ between persons with MS and controls. This indicates that the rate (i.e., slope) that persons with MS scanned their working

memory did not differ from controls. Janculjak and colleagues (1999) did, however, find persons with MS to have considerably slower scanning time overall (even though the slope did not differ). Overall slower scanning time on this task (i.e., the zero-intercept) would be captured by the measures Item Memory – Mean RT and Item Memory – Target Absent Effect in the current study, which did differ between groups even after accounting for differences in baseline RT between MS and controls. These measures capture the time it takes to complete all the steps in providing a response (e.g., perceiving and identifying the stimulus, initiating the scan of working memory, deciding whether the target is present, making a motor response), whereas slope gives the time it takes to scan working memory per additional item included in working memory. However, in the current study baseline RT (i.e., Simple RT Task – Mean RT) was factored out of the remaining DalCAB measures. The Simple RT Task captures the time it takes to perceive and identify a stimulus, then make a motor response. In addition, Choice/Simple RT Task – Decision Speed (RT), described in the vigilance network above, did not differ between MS and controls and therefore these differences (in Item Memory – Mean RT and Item Memory – Target Absent Effect) are likely not due to increased decision-making time. What remains is that persons with MS were slower at initiating the scan of their working memory (i.e., different zero-intercept). These results are opposite to those found by Archibald and Fisk (2000), who administered a Sternberg item memory task to 20 persons with relapsing-remitting MS (RRMS; EDSS *M* = 2.7, SD = 1.0) and 35 controls. These authors did not find the zero-intercept to differ between persons with RRMS and controls, however, the slope

of their working memory scanning time did differ. Although the sample collected by Archibald and Fisk (2000) had a similar level of neurologic disability as the current study (EDSS *M* = 1.9, SD = 1.0), and both studies had non-repeating memory sets, the Sternberg item memory task by Archibald and Fisk (2000) was much longer (30 minutes to complete) than the DalCAB Item Memory (less than 10 minutes), which may have made it difficult for participants to remain vigilant for the entire task (in the case of the Sternberg item memory) or may not have been enough trials at each set size to detect set size differences (in the case of the DalCAB Item Memory).

Go-No-Go Task.

Of the three Go-No-Go Task measures associated with the executive control network, only one differed between the MS and control groups: 20% Go Percent False Alarms. Yet, it was the control group who had more false alarms on average (0.5% MS versus 1.0% controls). No between group differences were found for the 80% Go Percent False Alarm measure. Similarly, studies by both Bonnet and colleagues (2010), and Covey and Shucard (2016), did not find error rate differences between persons with MS and controls on Go-No-Go tasks requiring 70% “go” responses. False alarms are understood to represent a lapse in response inhibition, especially when “go” responses are frequent and “no” responses are infrequent (Carter, Russell, & Helton, 2013). This connection between false alarms and response inhibition was evident in the previous factor analysis of the DalCAB, whereby the 80% Go Percent False Alarms had a higher loading with the with “inhibitory control” factor (p. 5, Table 3), compared to the 20%

“go” condition (Jones et al., 2015). Wilson, Finkbeiner, de Joux, and Russell (2016) examined a series of go-no-go tasks with different proportions of “go” responses in healthy adults from 0.50 to 0.95. The authors showed a relationship between RT and false alarms whereby individuals had faster RTs yet more false alarms as the proportion of “go” responses increased. Given that the control group were faster than MS participants in the current study, this may have led to more false alarms (i.e., higher 20% Go Percent False Alarms in the control group). Lastly, the 80% Vigilance Decrement, the change in RT between the last 1/3 and first 1/3 of trials in the 80% “go” condition, did not differ between groups. Collectively, these results suggest that the MS group did not exhibit a greater increase in their RT from the beginning to the end of the task or deficits in inhibitory control compared to controls. Indeed, it was the control participants who had more false alarms compared to the MS group when the requirement for a “go” response was infrequent.

Vertical Flanker Task.

The sole DalCAB measure from the Vertical Flanker Task associated with any of the attention networks was the Congruency Effect (Accuracy), which did not differ between MS and controls. For the DalCAB, only Congruency Effect (Accuracy) was associated with the executive control network in the Jones and colleagues (2015) factor analysis and hence is used in the current analyses, however, the congruency effect is typically examined with regards to RT. The congruency effect is when individuals are slower to respond to a central target when it is flanked by incongruent stimuli (e.g.,→ ← →). This effect is observed in

healthy adults (using the ANT: Ishigami & Klein, 2010) and is exaggerated in persons with dementia (Krueger et al., 2009). Covey and Shucard (2016) were able to observe the congruency effect in a sample of 15 persons with MS and used event-related potentials (ERPs) to examine the associated cognitive control processes. The MS group's ERPs suggested delays in activating selective attention and conflict monitoring, which are cognitive processes commonly associated with a flanker task. Based on the current DalCAB results, these processes were not affected in our sample of persons with MS. Covey and Shucard (2016) did not find the congruency effect to differ between MS and controls in their behavioural RT data, which suggests that despite not finding a behavioural difference in the current sample, deficits in cognitive processing may be occurring. Covey and Shucard (2016) did include individuals with progressive subtypes of MS ($n_{progressiveMS}$ = 5) in their sample, however, and the current study is entirely persons with RRMS.

Choice and Dual RT Tasks.

Choice RT Task – Switch Cost (Accuracy) did not differ between MS and control groups, however, Dual Task – Cost (RT; which is computed by comparing RT between the Choice RT Task and Dual Task) did differ between groups. In previous factor analysis work on the DalCAB both of these measures were associated with the same factor, indicating that the process to accurately switch between two responses (as in the Choice RT Task) and the process to quickly switch between two tasks (as in the Dual Task) are related (Jones et al., 2015). Persons with MS have been shown to perform less accurately compared to

controls when completing a dual task compared to a single task (D'Esposito et al., 1996). Although similar to the current study, Stoquart-ElSankari and colleagues (2010) did not find differences in error rates between MS and controls on a choice RT task, the authors did not break down their results into switch and non-switch trials. The cognitive process that leads to a behavioural “switch cost” are still a matter of debate, but potentially represent a proactive interference given the type of task used in the DalCAB (Kiesel et al., 2010). Dual Task – Cost is represented by slower RTs that are attributed to interference of the second task or increase in attentional load (Jones et al., 2016). Given that the previously described Item Memory Task measures relating to attentional load did not differ between groups [i.e., Set Size Effect (Accuracy) and Set Size Effect (RT)], differences in Dual Task – Cost, which require switching between tasks (instead of switching between responses, as in Choice RT Task), likely represents a greater interference effect from a second task in the MS group compared to controls. Slower RT in a dual task is also seen in other neurologic disorder populations, such as Alzheimer’s disease (Della Sala, Cocchini, Logie, Allerhand, & MacPherson, 2010).

3.3.3 Orienting Network

Persons with MS differed from the control group on two of the three measures associated [in the original Jones and colleagues (2015) factor analysis] with the orienting network, even after accounting for baseline RT differences between groups. Based on the aspects of the orienting network that differed between groups, this MS sample: (1) had reduced ability to quickly search their visual field for a target, and (2) were differentially affected by an increase in the

size of their visual search (i.e., RT slowed as distractor items were added more so than for control participants). Our MS sample showed intact ability to disengage and re-orient their attention over time, compared to the control group. These differences are discussed more thoroughly, by task, below.

Visual Search Task.

Both of the Visual Search Task measures associated with the orienting network differed between the MS and control groups: Conjunction Search – Mean RT and Conjunction Search – Set Size Effect (RT). Utz and colleagues (2013) similarly found their sample of persons with RRMS to differ from controls in RT on a conjunction search task, as well as a feature search task as discussed above. Contrary to a feature search task where a target must simply be detected, in a conjunction search task the target shares some characteristics with the distractors and does not immediately jump out. These similarities mean the individual must use attentional control to guide their search for the target, resulting in slower RTs for bigger set sizes (i.e., there is more to search through; Treisman & Gelade, 1980). For the current study, this indicates that the participants with MS were slower overall to search for a visual target and were differentially affected by an increase in the size of their search (i.e., both the zero-intercept and slope of visual search time differed between groups).

Go-No-Go Task.

The Go-No-Go Task – Proportion Effect (RT; i.e. the difference in RT between the 80% “go” and 20% “go” conditions) did not differ between MS and control groups. Wilson and colleagues (2016) demonstrated that RTs became

faster and accuracy decreased as the proportion of “go” responses increased, in their comparison of go-no-go tasks requiring 50%, 65%, 80%, and 95% “go” responses, in a sample of healthy adults. In previous factor analysis of the DalCAB, the Go-No-Go Task – Proportion Effect (RT) was associated with the same factor as the Visual Search Task Conjunction Search measures discussed above (Jones et al., 2015) and was hypothesized to reflect participants disengaging their attention for some part of each trial and re-orienting when a “go” target was again presented. Thus, for the current study, MS participants and controls did not appear to differ in their ability to disengage and re-orienting their attention over time.

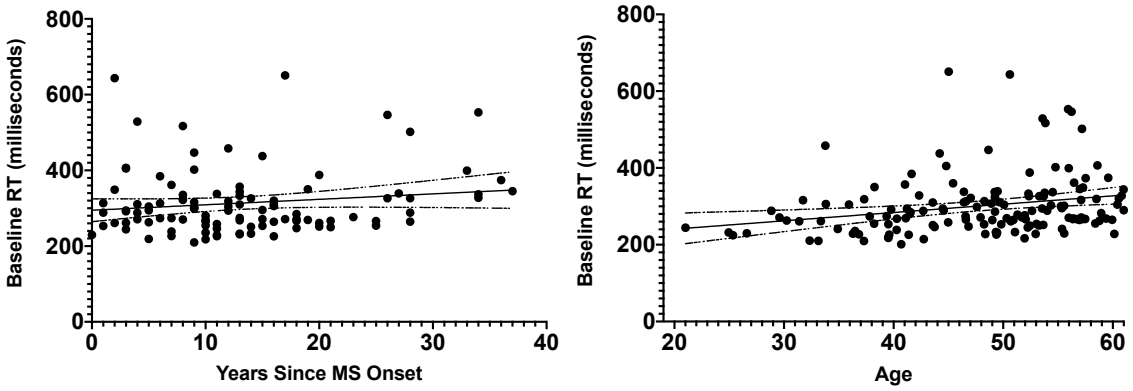
3.3.4 DalCAB Performance and Clinical Characteristics

DalCAB performance was associated with both patient outcomes that were examined: EDSS and health-related quality of life (HRQoL) as measured by the Health Utility Index (HUI). EDSS was associated with baseline RT as well as the vigilance network, specifically target detection (Visual Search Task Feature Search – Mean RT) and maintaining consistency in responses (Choice RT Task – Standard Deviation). This was the case even though variation due to baseline RT differences between groups was removed from the DalCAB measures. HRQoL on the HUI was associated with the same DalCAB measures as EDSS, plausibly because EDSS and HRQoL on the HUI were moderately correlated with each other, consistent with previous work by Fisk and colleagues (2005). In the current study, HRQoL on the HUI was also associated with the orienting network (slower overall to visually search for a target; Visual Search Task Conjunction Search –

Mean RT). This was the only unique association between HRQoL on the HUI and the DalCAB measures.

Years since MS onset was associated with performance across all three attention networks. Yet, only one measure of each the vigilance and executive control networks were associated, both of these measures coming from the Dual Task: maintaining consistency in responses (Dual Task – Switch Cost) and difficulty switching between responses when attention was divided between two tasks (Dual Task – Cost), respectively. Baseline RT did not increase as years since MS onset increased, and instead appeared to remain relatively stable across disease durations (see Figure 4). This suggests that slowed RT in MS is a feature present at disease onset and remains relatively constant throughout disease course, however, attention network performance decreases over disease course.

Figure 4. Baseline RT as a Function of Years Since MS Onset and Participant Age.



Note. Left Figure: Depicting the non-significant correlation between baseline RT (i.e., Simple RT Task – Mean RT) and years since MS onset (MS group only, *n* = 104); Right Figure: Depicting the significant correlation between baseline RT and participant age (full sample, *n* = 144). Solid line represents the line of best fit, with a 95% confidence interval represented by the dashed lines.

Age was associated with baseline RT (See Figure 4). Age was also associated with performance across all three attention networks, after accounting

for variance due to baseline RT. These correlations suggest that as someone ages their RT increases and their attentional abilities decrease. This is consistent with baseline RT increasing with age in the general population (Godefroy, Roussel, Despretz, Quaglino, & Boucart, 2010). As age did not differ between the MS and control groups, it would not account for the discrepancies in attention network performance between groups. Godefroy and colleagues (2010) examined the origin of age-related increase in RT and suggested that slowed RT in individuals less than 60 years of age (i.e., the age group of the current study) was due to perceptuomotor changes (i.e., more time required to visually inspect stimuli and slower finger tapping speed) and not attentional decline. This is perhaps consistent with the current study, as significant correlations in the entire sample between age and attention network measures were present but weak (r = .128 to .287).

3.3.5 DalCAB Performance and Standard Neuropsychological Tests

Baseline RT (Simple RT Task – Mean RT) was associated with all standard neuropsychological test scores, except CVLT-II Trial 1, which was not associated with any DalCAB measures. While the remainder of the DalCAB measures had the variability due to baseline RT removed, SDMT Total was still associated with performance measures from all three attention networks. This provides support for the SDMT as a test which reflects not only information processing speed, but also attention (Amato et al., 2010; Reuter et al., 2011; A Ruet et al., 2013).

The associations observed between other standard neuropsychological tests and DalCAB performance provide indications of the roles that attention abilities play in completing these tasks. For example, for COWAT Semantic Total,

individuals are asked to name as many items they can think of in 60 seconds belonging to a particular semantic category. In the current study, lower COWAT Semantic Total was associated with both having more lapses in sustained attention (Go-No-Go Task – 20% Go Percent False Alarms) and being slower to initiate the scanning of items held in working memory (Item Memory Task – Mean RT). One could postulate that in the current sample of MS study participants, individuals who experienced lapses in their sustained attention over the 60 seconds of the COWAT Semantic Total and were slower to scan information held in their memory for relevant items belonging to the category would indeed have lower verbal fluency scores.

3.3.6 Standard Neuropsychological Test Performance

Between-group comparisons of the standard neuropsychological test scores were completed. These did not address specific aims of the current thesis as described above but were conducted in order to allow comparisons with previous MS literature.

Persons with MS had worse performance on all scores associated with the standard neuropsychological tests with one exception: BVMT-R Total Immediate Recall. When comparing rates of individuals in each group who met criteria for "cognitive impairment" on a task (i.e., z = -1.5), persons with MS had higher rates of impairment on the SDMT Total, CVLT-II Total Immediate Recall, and COWAT Total. These tasks are commonly referred to as tests of information processing speed, verbal learning and memory, and verbal fluency, respectively. Yet deficits in a variety of other cognitive domains can affect performance on these tests:

visual scanning, tracking, and incidental memory (SDMT Total), working memory (CVLT-II Total Immediate Recall), psychomotor speed and executive functioning (COWAT Total; Strauss, Sherman, & Spreen, 2006). Prevalence of impairments in the MS group for an individual domain was as high as 23.1%, indicating that these individuals who are classified as “low neurologic disability” using EDSS still experience cognitive impairments. This discrepancy has also been found by others who have examined cognition in persons with MS and low EDSS scores (DiGiuseppe et al., 2018).

The proportion of people impaired on LNS Total did not differ between groups, in addition to the BVMT-R Total Immediate Recall. Only one person in the MS group (0.96% of the sample) and none in the control group were impaired on the task, which is typically considered to assess working memory. This is below the percentage of individuals expected to fall -1.5 SD below the mean in the general population, based on the normal curve (i.e., 7%). Various groups have previously identified working memory deficits in persons with MS using different methods (Archibald & Fisk, 2000; Lengenfelder et al., 2006; Ruchkin et al., 1994). A study by Berrigan and colleagues (2013), also found that LNS Total differed between control participants and MS participants with low EDSS (M_{EDSS} = 1.83), with a medium effect size (Cohen’s d = 0.45). However, another recent study found the proportion of persons with MS impaired on the LNS test fell below what would be expected in the general population (derived from graph; MS sample n = 255; Whitehouse et al., 2019). Others have also found the LNS test to classify fewer persons with MS as impaired than other working memory tests (DeLuca et al.,

2004). Therefore, LNS appears to be variable in its sensitivity to working memory deficits, and future work in MS should use a more reliable task to assess this cognitive domain.

Unexpectedly, the number of control participants impaired on the BVMT-R Total Immediate Recall exceeded that of the MS group and exceeded that which would be expected in the general population based on the normal curve (i.e., 7%). Ten control participants (25%, vs 22.1% in the MS group) met the criteria for impairment using both Canadian-based norms adjusted for age, sex, and years of education (Walker et al., 2017) as well as the published American-based norms adjusted for age (Benedict, 1997). The BVMT-R is commonly recommended for inclusion in cognitive test batteries designed for people with MS, on the basis of its psychometric properties and associations with MRI outcomes (Langdon et al., 2012). The BVMT-R was included in four of the five neuropsychological batteries highlighted by the International Multiple Sclerosis Cognition Society (Benedict et al., 2016). Although it is unclear based on aggregate data why the control group of the current study had a high rate of impairment on this task, visual inspection of the control participant's data suggested that some control participants lost points for inaccuracy on their drawing of the target figures, despite appearing to adequately recall the figures. This could be due to some control participants not understanding the importance of accurately drawing the details of the figures they were shown.

In summary, the current analyses have shown that attention network performance differs between persons with MS and control participants (aim 1).

Aspects of all three attention networks were found to differ between groups. Known groups validity, ecological validity, and concurrent validity was demonstrated for the DalCAB (aim 2). In the final analyses conducted for completeness, between-group comparisons confirmed that cognitive impairments in the current MS group are present based on standard neuropsychological tests.

3.3.7 Implications, Limitations, and Future Research

Multiple variables were used to capture performance on each of the three attention networks assessed by the DalCAB, allowing for detailed analyses of attentional abilities in this population. This novel assessment measure moves away from using the total score on one test to represent the functioning of an entire cognitive domain (e.g. attention, memory) and may provide insights into the variability in the literature on cognitive functioning in MS.

Wojcik and colleagues (2019) conducted a systematic review on available computerized cognitive tests used in persons with MS. The authors evaluated whether each computerized cognitive test had associated research covering four different types of validity as they pertained to an MS population, given that a previous review had highlighted the lack of validity and reliability studies for computerized tests in MS (Lapshin et al., 2012). The current study demonstrates initial validity of the DalCAB in an MS population consistent with three types of validity as defined by Wojcik and colleagues (2019): (1) discriminant or known groups validity – “MS and [health controls] compared by [a] statistical test for difference between means”, (2) ecological validity – “association between [the] test and relevant patient outcomes”, such as EDSS, and (3) concurrent validity –

“comparing [the computerized neuropsychological assessment] and conventional [neuropsychological tests]” (p. 1849).

Research has moved toward developing computerized cognitive assessment tasks for MS to reduce the time and resource demands required of neuropsychological assessments in an MS clinic. Even the relatively brief SDMT, the sole cognitive test recommended as a core assessment test in the MS Common Data Elements Recommendations (National Institute of Neurological Disorders and Stroke, 2011), has been developed into a computer tablet-based format (Akbar, Honarmand, Kou, & Feinstein, 2011). The DalCAB is the first computerized battery that focuses entirely on attentional abilities to be used in an MS population [according to the review by Wojcik and colleagues (2019)], other than the ANT.

The current analyses have limitations. MS and control participants differed on WTAR Total, with the MS group having significantly lower WTAR Total scores. The WTAR is considered a means of estimating an individual’s premorbid level of cognitive functioning (i.e., functioning prior to the onset of injury or disease) based on reading level for atypically spelled words. Although the MS and control groups were matched on levels of education, differences in estimated premorbid intellectual functioning could be considered to represent a limitation of the current analyses. Thus, between-group comparisons of the standard neuropsychological tests were repeated with the variability due to the WTAR Total removed (i.e., parceled out using regression analyses). In these analyses, the same standard neuropsychological test scores continued to differ between groups even with

variation due to WTAR Total accounted for, with the exception of BVMT-R Long Delay Free Recall. The other BVMT-R score (Total Immediate Recall) was the only test score that did not differ between groups originally. When comparing proportions of persons impaired, the control group continued to exceed the proportion of individuals that would be expected to be impaired based on the normal population distribution (expected: 7% impaired, current control group: 25% impaired). Taken together, these analyses suggest statistical differences in WTAR Total performance do not explain the variability in cognitive performance between groups, however, performance on the BVMT-R in the current sample did not conform to expected levels for a representative sample of the control population.

Of the standard neuropsychological tests used in the current study, none are designed to assess attention abilities specifically. Direct comparison between standard tests of attention would be more in line with providing concurrent validity for the DalCAB. However, the absence of an existing cognitive testing battery of attention properly validated in MS and commonly used in clinical practice prohibited such a comparison. Instead, the DalCAB was compared with standard neuropsychological tests recommended for regular clinical use in MS.

Lastly, discrepancies between cognitive testing in optimal environments and reported real-world cognitive difficulties have been highlighted as a key priority for MS research (Sumowski et al., 2018). The current study did not include any cognitive tests designed to reflect real-world tasks, such as dispensing medications. Future research examining the DalCAB in an MS population should examine existing real-world cognitive tasks and additional relevant patient

outcomes such as employment status. The current sample of persons with MS was mostly individuals whose first language was English (96.2%) and data regarding ethnicity was not collected. A body of literature is emerging showing that African American women with MS have a more aggressive course of disease, and there a fewer studies of the impact of MS in this group (Stuifbergen et al., 2020). Future work should seek to examine whether the DalCAB would be an appropriate tool for ethically, culturally, and linguistically diverse groups, considering the stimuli for the DalCAB (i.e., playing cards) were chosen with these applications in mind.

Chapter 4. Attention Network Performance and Intra-Individual Variability in Persons with MS Not Impaired on Standard Neuropsychological Tests

4.1 Background

In the past 30 years, cognitive dysfunction has developed into a widely recognized issue in MS and the availability of research in this area has continued to grow. Yet the need for time and resource efficient cognitive tasks that overcome the barriers of incorporating neuropsychological assessment into everyday clinical practice are still being investigated. Cognitive tasks that meet this need have been highlighted as a priority in work on cognition in MS (Sumowski et al., 2018). The DalCAB, which does not require specialized neuropsychological training or equipment, and provides numerous measures of attention that are combined into three latent variables, is a promising option for assessing cognition in MS clinically.

Given the variability in symptoms, disease progression, and prognosis among persons with MS (Eriksson et al., 2003; Koch et al., 2008), cognitive assessment tools that allow clinicians to detect subtle changes in cognitive function are necessary. Identifying who will and who will not respond to a specific disease modifying drug for MS is challenging, as many individual characteristics, such as age, sex, and disease duration may not differ between drug responders and non-responders (e.g., Río et al., 2006, for the drug interferon-beta). Treatment decisions made by clinicians are based on available client information such as level of neurologic disability, however, the most common scale for classifying neurologic disability, EDSS, is biased toward motor functioning. Identifying

cognitive changes provides clinicians additional information that can inform MS treatment decisions. In addition, identifying these cognitive differences between persons with MS is a step towards explaining some of the variability in prognosis between individuals and can inform future work regarding treatment efficacy. Although batteries of standardized neuropsychological tests have been complied for use with persons with MS, such as the Brief Cognitive Assessment of Multiple Sclerosis (BICAMS; Langdon et al., 2012), it is unclear if cognitive changes occur undetected by these tests in individuals who otherwise have low neurologic disability.

Although the majority of computerized tests rely on mean-level differences in RT to evaluate performance, within-subject variability or intra-individual variability (IIV) has shown promise as a sensitive indicator of neurologic dysfunction in a variety of clinical populations (Geurts et al., 2008; Stuss et al., 2003). Increased IIV indicates poor consistency in an individual's responses and is thought to be "a behavioural indicator of central nervous system (CNS) integrity" (p. 475, MacDonald et al., 2006). Initial work on IIV in MS populations has found IIV to be increased in persons with MS, indicating that persons with MS have less consistency in their responses (Wojtowicz et al., 2012; Wojtowicz et al., 2013). These differences between persons with MS and controls are noted even when overall slowed RT due to MS is accounted for. Computerized assessment measures allow for IIV to be calculated by virtue of measuring response times over repeated trials of the same or similar tasks, therefore, IIV can be calculated for each DalCAB task.

The aims of the analyses described in this chapter were to (1) examine whether differences in mean-level RT variables on the DalCAB were found between persons with MS who were not impaired on standard neuropsychological tests used clinically (i.e., “unimpaired”) and controls, and (2) examine whether IIV calculated for each of the DalCAB tasks differed between “unimpaired” persons with MS and controls. To address aim (1), persons in the MS sample who were classified as “unimpaired” on the standard neuropsychological tests included in the BICAMS were selected (*4.2.1 Selecting Persons with MS Not Impaired on Standard Neuropsychological Tests*). These unimpaired persons with MS were then compared to the control group on attention network performance as measured by the DalCAB tests (*4.2.2 DalCAB Performance in “Unimpaired” Persons with MS*). Prior to addressing aim (2), two measures of IIV were calculated (coefficient of variation and individual standard deviation) from each of the DalCAB tests and these measures were compared between the entire MS sample and control participants (*4.2.3 Differences in Intra-Individual Variability Between Groups*). Only measures of IIV that differed between the entire MS sample and control participants were used for the remaining analyses in this thesis. This was the same approach that was used previously to examine the measures of attention network performance on the DalCAB in Chapter 3 (*3.2.4 Differences in Attention Network Performance Between Groups – Known Groups Validity*). Then, to address aim (2), persons in the MS sample who were classified as unimpaired on the standard neuropsychological tests included in the BICAMS were compared on IIV (*4.2.4 Intra-Individual Variability in “Unimpaired” Persons with MS*). For

completeness, exploratory analyses to examine the associations of IIV with the standard neuropsychological tests, general demographics, and the MS participant's clinical characteristics were also conducted (*4.2.5 Associations Between Individual Standard Deviation and Standard Neuropsychological Tests* and *4.2.6 Associations Between Individual Standard Deviation and Clinical Characteristics*).

It was hypothesized that attention network performance would differ between unimpaired persons with MS and controls, given that previous work on attention network performance in MS using the Attention Network Test (ANT) identified differences in attention networks, despite relatively unpaired samples on standard neuropsychological tests (Urbanek et al., 2010). The nature of these differences was uncertain, given the mixed results in previous work in MS populations using the ANT. Although IIV has not been previously compared between persons with MS not impaired on standard neuropsychological tests, the measure has been shown to differ between persons with MS even when differences in baseline RT are accounted for, and in groups of persons with MS low neurologic disability based on EDSS (Wojtowicz et al., 2012; Wojtowicz et al., 2013). Therefore, we hypothesized that it would also differ between unimpaired persons with MS and controls.

4.2 Data Analyses and Results

4.2.1 Selecting Persons with MS Not Impaired on Standard Neuropsychological Tests

The BICAMS is a group of neuropsychological tests recommended for use in clinical practice to detect cognitive impairments in persons with MS (Kalb et al., 2018). Test scores included in the BICAMS are: the total number of correct responses on the SDMT (i.e., Total Score), the total number of correct responses across the five immediate recall trials of the CVLT-II (i.e., Total Immediate Recall), and the total number of correct responses across the three immediate recall trials of the BVMT-R (i.e., Total Immediate Recall). The subsequent analyses selected persons with MS who were not impaired (i.e., no z-score < -1.5) on the test scores comprising the BICAMS. These persons with MS who were not impaired on the BICAMS were referred to as the "unimpaired" MS group. DalCAB performance of the unimpaired MS group was compared to control participants to determine if the DalCAB was able to identify cognitive changes that are likely to be undetected in routine clinical practice for persons with MS. Of the total MS group, 65 persons with MS were unimpaired on all BICAMS scores. This unimpaired MS group did not differ from the control group with regard to age, years of education, or gender. The unimpaired MS group included the full range of EDSS scores (i.e., 0 to 4.5) of the total MS group (n = 104) although the mean EDSS score was lower in the unimpaired MS group (M = 1.6 versus 1.9). Years since MS onset and percentage of participants on disease modifying drugs were very similar for the unimpaired MS

group and total MS group. See Table 11 for more details regarding the characteristics of the unimpaired MS group.

Table 11. Characteristics of MS Participants Not Impaired on the BICAMS (Unimpaired MS Group).

Characteristic	**Control Group**	**Unimpaired MS Group**	**Statistical Comparisons**
N	40	65	
Sex, n (%)			
Female	36 (90.0)	57 (87.7)	X^2 (1) = 0.130, p = .718
Male	4 (10.0)	8 (12.3)	
Age, mean (SD)	49.4 (9.6)	46.1 (9.1)	t(79.2) = -1.7, p = .085
Years of education, mean (SD)	15.1 (1.5)	14.8 (1.9)	t(97.6) = -1.0, p = .324
	MS Group	**Unimpaired MS Group**	
N	104	65	
EDSS score, mean (SD)	1.9 (1.0)	1.6 (0.9)	These comparisons were not made as the unimpaired MS group is 62.5% of the same participants as the total MS group.
Years since onset, mean (SD)	13.3 (8.8)	11.9 (8.1)	
On a disease modifying drug, n (%)	85 (81.7)	51 (78.5)	

4.2.2 DalCAB Performance in "Unimpaired" Persons with MS

One Analysis of Variance (ANOVA) was used to compare the unimpaired MS group and controls on the Simple RT Task – Mean RT, to evaluate whether baseline RT alone could be used for detecting early cognitive changes in persons with MS.

Three Multivariate Analysis of Variance (MANOVA) models were used to compare DalCAB performance relating to the (1) orienting, (2) vigilance, and (3)

executive control networks between the unimpaired MS group and controls. As described in *Chapter 3.2.6 (Accounting for Slowed RT in MS on the DalCAB)*, linear regression was used to parse out the variation in DalCAB measures accounted for by baseline RT differences between groups (Simple RT Task – Mean RT), leaving unstandardized residual DalCAB scores. These unstandardized residual scores were used in all DalCAB analyses described below. As an exception, the Go-No-Go Task – 20% Go Percent False Alarm variable was used without removing variation due to baseline RT, as it is a variable based on accuracy not speed.

See Table 12 for results of the ANOVA model and all MANOVA models. Simple RT Task – Mean RT differed between groups. Unimpaired MS participants differed from controls on DalCAB measures of vigilance and executive control, but not orienting. Of the 3 DalCAB variables associated with the vigilance network, only Dual Task – Switch-Cost made a significant unique contribution to the model. Of the 4 DalCAB variables associated with the executive control network, the Go-No-Go Task – 20% Go Percent False Alarm and the Dual Task – Cost both made significant contributions to the model.

Table 12. Attention Network Performance for Unimpaired Persons with MS Compared to Controls.

Model	**Overall (M)ANOVA**	**Effect Size**	**Individual Dependent Variables Included in the Model**	**Effect Size**
Simple RT Task	$F(1,103) = 6.939$, $p = 0.010$	.063	Not applicable as an ANOVA has only one dependent variable	

Model	Overall (M)ANOVA	Effect Size	Individual Dependent Variables Included in the Model	Effect Size	
Orienting	Pillai trace=.034, $F_{2,101}$=1.789, p=.172	.034	Visual Search Conjunction Search – Mean RT Visual Search Conjunction Search – Set Size Effect (RT)	Not examined as overall model was not significant	
Vigilance	Pillai trace=.081, $F_{3,99}$=2.904, p=.039	.081	Visual Search Task Feature Search – Mean RT	$F(1,101) = 2.380$, $p = .126$	.023
			Dual Task – Switch-Cost	$F(1,101) = 5.565$, $p = .020$	.052
			Choice RT Task – Standard Deviation	$F(1,101) = 3.415$, $p = .068$	.033
Executive Control	Pillai trace=.101, $F_{4,99}$=2.786, p=.031	.101	Go-No-Go Task – 20% Go Percent False Alarm	$F(1,102) = 4.633$, $p = .034$	.043
			Item Memory – Mean RT	$F(1,102) = 1.728$, $p = .192$	.017
			Item Memory – Target Absent Effect (RT)	$F(1,102) = .693$, $p = .407$	.007
			Dual Task – Cost	$F(1,102) = 5.825$, $p = .018$	.054

Note. Significant F-tests and associated variables are shaded; All values remained significant after Benjamini-Hochberg correction for multiple comparisons; Reported effect size is partial eta squared (η^2_p).

4.2.3 Differences in Intra-Individual Variability Between Groups

Data Preparation

Intra-individual variability (IIV) has shown promise as a measure of subtle cognitive change in MS. IIV on DalCAB tasks was examined using two methods: coefficient of variation (CoV) and individual standard deviation (ISD).

Calculating Measures of IIV

The CoV and ISD were calculated for each participant on each of the 7 DalCAB tasks, however, the Visual Search Task was separated into its feature search and conjunction search trials given that these two types of trials were associated with different aspects of attention (i.e., vigilance and orienting networks, respectively) in the initial factor analysis of the DalCAB measures by Jones and colleagues (2015). Thus, there were 8 CoV variables and 8 ISD variables per participant. IIV variables were not divided into attention networks, as was done for the DalCAB measures, because each of the IIV variables are associated each with one DalCAB task while measures calculated from each DalCAB task can be associated with multiple attention networks [as shown in *Chapter 3.2.4* (*Differences in Attention Network Performance Between Groups – Known Groups Validity*)]. Therefore, attributing IIV from one DalCAB task to only one specific attention network was considered inappropriate at this stage.

CoV was calculated by taking the standard deviation of RT on the correct trials for each individual on each task and dividing that by the mean of the RT of correct trials on that task. ISD was calculated using standardized residual scores of RT for each individual on each task, whereby systematic differences in RT due

to trial (e.g., learning to learn) and group membership (e.g., MS versus control group as MS participants had slower RTs overall) were parcelled out. Standardized residual scores (i.e., z-scores) were then converted to t-scores [formula: t-score = (z-score * 10) + 50]. Finally, ISD represents the standard deviation of these t-scores (Hultsch et al., 2000). The DalCAB has built-in cut-off time limits in which participants must respond, and RTs less than 100ms are coded as "anticipatory", as described in *Chapter 3.2.2 (Data Cleaning)*. Imposing these cut-offs represents a conservative method for calculating IIV as extreme values are not included. As both CoV and ISD are considered to account for baseline RT differences in their calculation (Wojtowicz et al., 2012), no additional steps were taken to remove baseline RT from these measures.

Differences in IIV Between Total MS Group and Control Group

Eight ANOVA analyses were run to compare CoV between the total MS group and control group, as was done for the DalCAB variables in *Chapter 3.2.4 (Differences in Attention Network Performance Between Groups Between Groups – Known Groups Validity)*, prior to examining IIV in the unimpaired MS group. The 8 ANOVA correspond to one ANOVA for the CoV of the DalCAB tasks, with the Visual Search Task divided by feature search and conjunction search trials. Another 8 ANOVA analyses were run to compare ISD between the total MS group and control group. Each the ANOVAs included group membership (MS vs control) as the independent variable. As such, each ANOVA model was asking whether CoV or ISD for that DalCAB task differed between the MS and control groups.

All ANOVA results for CoV and ISD measures are listed in Table 13. For the 8 measures of CoV, only CoV on the Choice RT Task and Visual Search Task Conjunction Search differed between the MS and control groups. For the 8 measures of ISD, 6 differed between MS and control groups. Only ISD for the Go-No-Go Task and Item Memory Task did not differ between groups.

Table 13. Differences in IIV Between MS and Control Groups.

IIV Measures	**Does the MS group significantly differ from control?**	**Effect Size**
Coefficient of Variation (CoV)		
Simple RT	$F(1,142) = .066$, $p = 0.797$	.000
Choice RT	$F(1,142) = 8.646$, $p = 0.004$	.057
Go-No-Go	$F(1,142) = .513$, $p = 0.475$	.004
Dual Task	$F(1,138) = 3.218$, $p = 0.075$	.023
Item Memory	$F(1,142) = .013$, $p = 0.909$	.000
Vertical Flanker	$F(1,142) = .333$, $p = 0.565$	.002
Visual Search – Feature	$F(1,141) = 2.394$, $p = 0.124$	.017
Visual Search – Conjunction	$F(1,141) = 8.449$, $p = 0.004$	.057
Individual Standard Deviation (ISD)		
Simple RT	$F(1,142) = 4.058$, $p = 0.046$	.028
Choice RT	$F(1,142) = 17.124$, $p < 0.001$	.108
Go-No-Go	$F(1,142) = 4.099$, $p = 0.045$	.028
Dual Task	$F(1,138) = 15.844$, $p < 0.001$	.103
Item Memory	$F(1,142) = 3.446$, $p = 0.065$	.024
Vertical Flanker	$F(1,142) = 7.195$, $p = 0.008$	.048
Visual Search – Feature	$F(1,141) = 4.656$, $p = 0.033$	.032

IIV Measures	Does the MS group significantly differ from control?	Effect Size
Visual Search – Conjunction	$F(1,141) = 14.462$, $p < 0.001$	.093

Note: A Benjamini-Hochberg correction was applied to the 9 significant correlations. Only the 8 values that remained significant are shaded above; Reported effect size is partial eta squared (η^2_p).

4.2.4 Intra-Individual Variability in "Unimpaired" Persons with MS

After the IIV variables that differed between the total MS group and control group were identified, the remaining analyses focused on the aim of comparing persons with MS not impaired on the BICAMS to controls. Given that only two CoV measures differed between MS and control groups, the remainder of the analyses examined only ISD.

Once again, persons with MS who were unimpaired on the BICAMS, and hence may not be identified as having cognitive changes in an MS clinic appointment, were selected (unimpaired MS group n = 65). The ISD of these unimpaired persons with MS were compared to controls to determine if ISD was able to identify cognitive changes in persons with MS that would be missed by standard neuropsychological tests. To reduce the number of comparisons, only ISD variables shown in *Chapter 4.2.3 (Intra-Individual Variability as a Measure of Cognitive Change in MS)* to differ between the total MS group and control group were used (6 variables): Simple RT Task – ISD, Choice RT Task – ISD, Dual Task – ISD, Vertical Flanker Task – ISD, Visual Search Task Feature Search – ISD, and Visual Search Task Conjunction Search – ISD. This same approach that was used when selecting which DalCAB variables to include in analyses in Chapter 3.

A MANOVA model was used to compare the 6 ISD variables of interest between the unimpaired MS group and controls. This MANOVA included group membership (MS vs control) as the independent variable and all ISD measures as dependent variables. See Table 14 for complete MANOVA results. The main MANOVA model differed between the unimpaired MS group and controls, indicating that overall, ISD measures differed between groups. Of the individual dependent variables included in the model, only Choice RT Task – ISD, Dual Task – ISD, and Visual Search Task Conjunction Search – ISD explained unique variance between groups.

Table 14. ISD Compared Between Unimpaired Persons with MS and Controls.

Overall MANOVA	**Effect Size**	**Individual Dependent Variables Included in the Model**		**Effect Size**
Pillai trace=.148, $F_{6,96}$=2.774, p=.016	.148	Simple RT – ISD	$F(1,101) = .984$, $p = .324$	.010
		Choice RT – ISD	$F(1,101) = 7.445$, $p = .008$	.069
		Dual Task – ISD	$F(1,101) = 8.470$, $p = .004$	.077
		Vertical Flanker – ISD	$F(1,101) = 1.914$, $p = .170$	.019
		Visual Search Feature – ISD	$F(1,101) = 3.650$, $p = .059$	.035
		Visual Search Conjunction – ISD	$F(1,101) = 7.436$, $p = .008$	.069

Note: Significant results are shaded. All results remained significant after applying a Benjamini-Hochberg correction for multiple comparisons; Reported effect size is partial eta squared (η^2_p).

4.2.5 Associations Between Individual Standard Deviation and Standard Neuropsychological Tests

Exploratory analyses to examine the associations between ISD and the standard neuropsychological tests were conducted. Spearman non-parametric correlations (two-tailed) were used to explore associations between ISD and all standard neuropsychological test scores. The majority of ISD variables were correlated with the majority of the neuropsychological test variables, with some exceptions. CVLT-II Trial 1 was only associated with one ISD variable: Vertical Flanker Task – ISD. Dual Task – ISD was not associated with any CVLT-II or BVMT-R variables, except CVLT-II Short Delay Free Recall. COWAT Phonemic Total was not associated with Simple RT Task – ISD or Vertical Flanker Task – ISD. All correlations are reported in Table 15.

Table 15. Correlations between ISD Variables and Neuropsychological Tests in Total Sample.

Neuropsychological Test Variables	**ISD Variables**					
	Simple RT	Choice RT	Dual Task	Vertical Flanker	Visual Search Feature	Visual Search Conjunction
SDMT						
Total	-.366	-.499	-.248	-.467	-.468	-.408
CVLT-II						
Trial 1	-.050	-.146	-.102	-.187	-.082	-.132
Total Immediate Recall	-.194	-.392	-.109	-.339	-.237	-.226
SD Free Recall	-.207	-.376	-.185	-.342	-.278	-.222
SD Cued Recall	-.214	-.305	-.097	-.287	-.238	-.185
LD Free Recall	-.224	-.324	-.161	-.346	-.308	-.194
LD Cued Recall	-.186	-.324	-.110	-.303	-.293	-.251
BVMT-R						
Total Immediate Recall	-.229	-.251	-.053	-.211	-.177	-.333
LD Free Recall	-.205	-.248	-.167	-.279	-.247	-.299

Neuropsychological Test Variables	ISD Variables					
	Simple RT	Choice RT	Dual Task	Vertical Flanker	Visual Search Feature	Visual Search Conjunction
COWAT						
Phonemic Total	-.103	-.199	-.179	-.159	-.222	-.207
Semantic Total	-.300	-.329	-.221	-.268	-.258	-.213

Note. Spearman non-parametric correlations; In this table SD = Short Delay, LD = Long Delay; Significant direct effects are shaded. All statistically significant results remained after Benjamini-Hochberg correction for multiple comparisons.

4.2.6 Associations Between Individual Standard Deviation and Clinical Characteristics

Exploratory analyses were conducted to examine the associations between ISD and clinical characteristics of the participants. Spearman non-parametric correlations (two-tailed) were used to explore associations between ISD, demographics (age, years of education – MS and control), health-related quality of life [single attribute utility score on the Health Utility Index (HUI) – MS and control], and clinical characteristics (EDSS, years since MS onset – MS group only). As years since MS onset and years since MS diagnosis were highly correlated ($r_s = 0.945$, $p < 0.001$), only years since MS onset was included in the analyses.

See Table 16 for all correlations. In the MS group, Simple RT Task – ISD, Choice RT Task – ISD, Vertical Flanker Task – ISD, and Visual Search Task Feature Search – ISD were correlated with EDSS. Only Visual Search Conjunction Search – ISD was correlated with years since MS onset. When examining general demographics relevant to all participants, age and self-report health-related quality

of life on the HUI were significantly correlated with all ISD variables. Years of education was correlated only with Dual Task – ISD and Vertical Flanker – ISD.

Table 16. Correlations between ISD Variables and Participant Characteristics.

Participant Characteristics	ISD Variables					
	Simple RT	Choice RT	Dual Task	Vertical Flanker	Visual Search Feature	Visual Search Conjunction
MS Group Only						
EDSS	.203	.344	.107	.249	.230	.186
Years since MS onset	.082	.059	.153	-.088	.081	.248
MS and Control						
Age	.265	.242	.190	.186	.194	.256
Years of education	-.139	-.155	-.206	-.215	-.045	-.101
HRQoL	-.167	-.357	-.203	-.251	-.232	-.264

Note. HRQoL = Health-related quality of life, represented by the HUI single attribute utility score; Shaded cells represent significant Spearman non-parametric correlations (two-tailed). All 19 significant correlations were jointly subjected to a Benjamini-Hochberg correction and remained significant.

4.3 Discussion

The analyses described in the current chapter examined whether differences in attention network performance (based on mean-level RT on the DalCAB), or intra-individual variability (IIV) on the DalCAB, were detected in persons with MS who were not impaired on standard neuropsychological tests used clinically.

4.3.1 Attention Network Performance in "Unimpaired" Persons with MS

Baseline RT (i.e., Simple RT Task – Mean RT) was slower for persons with MS who were not impaired on the Brief International Cognitive Assessment for MS (BICAMS; n = 65) compared to control participants (medium to small effect size),

confirming that even in persons with MS not impaired on standard neuropsychological tests, baseline RT differences between groups are still evident and should be accounted for.

Persons with MS not impaired on the BICAMS differed from age, years of education, and gender matched control participants in their performance on the vigilance and executive control networks overall (medium effect sizes for both networks). These disparities were evident despite baseline RT differences between groups having been accounted for. Although three DalCAB measures were included to represent the vigilance network, only Dual Task – Switch Cost (i.e., more difficulty maintaining consistency in responses in the MS group) made a significant contribution in accounting for the difference in performance between the groups. Although four DalCAB measures were included to represent the executive control network, only two variables made a significant contribution to the difference in performance between groups. (1) Go-No-Go Task – 20% Go Percent False Alarm, whereby the control group had more lapses in their sustained attention and (2) Dual Task – Cost, whereby the MS group had more difficulty switching between responses when attention was divided between two tasks. These results demonstrate that decreased attention network performance is evident in persons with MS who do not exhibit cognitive deficits on commonly used neuropsychological tests, even after accounting for slowed RT in MS.

4.3.2 Measures of Intra-individual Variability in Total MS Sample

Two measures of IIV were compared in the current study, individual standard deviation (ISD) and coefficient of variation (CoV). These were calculated

for each of the seven DalCAB tasks, with the Visual Search Task trials divided into feature search and conjunction search trials. These two IIV measures were chosen given their previous use in MS populations (Wojtowicz et al., 2012): CoV is a simpler computation that accounts for mean RT of each task. ISD is a more innovative calculation that accounts for learning effects over the course of a task as well as between group differences in baseline RT.

As was done with the DalCAB measures in *Chapter 3.2.4* (*Differences in Attention Network Performance Between Groups – Known Groups Validity*), measures of IIV were first compared between the entire MS sample (*n* = 104) and controls. ISD differed between the MS and control groups on six of the eight tasks, whereas only CoV on the Choice RT Task and Visual Search Task Conjunction Search differed between groups. As such, ISD was used for the remaining analyses. This is consistent with the previous work of Wojtowicz and colleagues (2012) who found MS participants had greater ISD than controls on three computerized RT tasks (i.e., a simple RT task, a choice RT task, and a semantic search RT task – where participants decide yes/no whether the presented word is part of a semantic category), yet CoV did not differ between groups on any of the tasks.

Differences in ISD between MS and control participants were greatest for the Visual Search Task Conjunction Search, Dual Task, and Choice RT Task, which were all medium sized effects. This is consistent with the results from previous analyses in *Chapter 3.2.4 (Differences in Attention Network Performance Between Groups – Known Groups Validity)*, which compared attention network

performance on the DalCAB between MS and control participants. In the previous analyses, both variables associated with Visual Search Task Conjunction Search differed between groups as did both variables associated with the Dual Task. Although the Choice RT Task – Switch-Cost (Accuracy) did not differ between MS and controls, Choice RT Task – Standard Deviation did. These results indicate that measures of ISD mirror performance overall on the DalCAB.

Unexpectedly, Simple RT Task – ISD did differ between groups although Simple RT Task – Standard Deviation, from *Chapter 3.2.4 (Differences in Attention Network Performance Between Groups – Known Groups Validity)*, did not. Simple RT Task – Standard Deviation is the individual standard deviation of the raw RTs and between group variation in baseline RT was removed using linear regression before further analyses. Whereas Simple RT Task – ISD is the individual standard deviation of the normalized RTs after the effects of group (i.e., baseline RT differences between MS and control participants) and trial (i.e., learning effects or boredom over the course of a task) have been parceled out. These results suggest that the variation due to trial created enough noise in the data that Simple RT Task – Standard Deviation did not differ between groups yet Simple RT Task – ISD, where variation due to trial is removed, did differ between groups (with a small effect size). These results indicate that accounting for variability due to learning effects over the course of the task (i.e., accounting for variation due to trial) is important, given that different results are obtained within the same sample when this is not accounted for.

4.3.3 Individual Standard Deviation in "Unimpaired" Persons with MS

Persons with MS who were not impaired on the Brief International Cognitive Assessment for MS (BICAMS; *n* = 65) differed from age, level of education, and gender matched control participants in their ISD on DalCAB tasks. ISD on the Choice RT Task, Dual Task, and Visual Search Task Conjunction Search all made significant contributions to explaining the overall difference in ISD between groups (medium to small effect sizes). Perhaps expectedly, these are the same three variables that had the largest effect sizes when comparing the entire MS sample (*n* = 104) to the control group. Existing work on measures of IIV have concluded that it is a behavioural indicator of overall CNS health (MacDonald et al., 2006), as IIV increases with age (Williams et al., 2005), is not affected by somatic disturbances such as pain (Hultsch et al., 2000), and is increased in neurologic populations such as traumatic brain injury (Stuss et al., 2003) and autism spectrum disorder (Geurts et al., 2008). In persons with MS specifically, ISD has been shown to reflect white matter structural integrity (Mazerolle et al., 2013). The current analyses indicate that ISD may be used to detect changes in the CNS affecting cognition in persons with MS who may not be identified by standard clinical tests.

4.3.4 Individual Standard Deviation and Standard Neuropsychological Tests

As was done for attention network performance, associations between ISD on each DalCAB task and standard neuropsychological tests were examined. The majority of ISD variables were correlated with the majority of standard neuropsychological test scores, with few exceptions. For example, Choice RT

Task – ISD, Visual Search Task Feature Search – ISD, and Visual Search Task Conjunction Search – ISD were associated with all 11 neuropsychological test variables, except CVLT-II Trial 1. Although there were many significant results, the majority were weak correlations (with some moderate correlations between the SDMT and ISD variables). The lack of specificity in the associations between the standard neuropsychological tests and ISD is further evidence that ISD is not measuring one specific cognitive process, but instead reflects overall CNS health. This is consistent with work by Mazerolle and colleagues (2013) who demonstrated that ISD on a simple RT task was associated with functional connectivity across more white matter fibre tracks than mean RT on the same task.

4.3.5 Individual Standard Deviation and Clinical Characteristics

In the total MS and control sample, increased age was associated with increased ISD on all tasks. Williams and colleagues (2005) demonstrated how ISD changes with age, examining 273 individuals aged 6 to 81 with no visual, hearing, and motor impairments. Williams and colleagues (2005) showed that ISD has a U-shaped trajectory: decreasing from childhood to young adulthood and increasing during adulthood. RT is known to increase with age (Godefroy et al., 2010) and baseline RT (i.e., Simple RT Task – Mean RT) was shown to be associated with age in Chapter 3 (*3.2.7 DalCAB Correlations with Clinical Characteristics – Ecological Validity*). As ISD accounts for differences in RT, these results together indicate that aging is associated with slower RT and more variability in those RTs.

Years since MS onset was associated only with Visual Search Conjunction Search – ISD, yet EDSS was associated with ISD on 4 of the tasks. This is in line

with ISD being a behavioral measure of overall CNS health, as disability due to MS increases at varying rates between individuals (Pittock et al., 2004). As such, EDSS is a better approximate of neurologic disability compared to years since MS onset. It is possible that the association between ISD and EDSS would have been stronger if the current sample had a greater range of EDSS scores (cut-off for the current analyses was 4.5, whereas EDSS can range from 0 to 10).

In summary, the current analyses showed that performance on vigilance and executive control attention networks differed between persons with MS who were not impaired on standard neuropsychological tests used clinically and control participants (aim 1). Measures of ISD, specifically on the Choice RT Task, Dual Task, and Visual Search Task Conjunction Search, were also shown to differ between persons with MS who were not impaired on standard neuropsychological tests and control participants (aim 2). In the final analyses conducted for completeness, ISD was shown to be associated with standard neuropsychological test scores broadly as well as to participant characteristics such as age and EDSS.

4.3.6 Implications, Limitations, and Future Research

Standard neuropsychological tests included in the BICAMS classified 39 persons in the current MS sample (37.5%) as impaired on at least one task. Therefore, as expected, many persons with MS reported to have low neurologic disability based on EDSS (i.e., the current sample) still experienced significant cognitive deficits.

The DalCAB - a computerized measure that does not required specialized neuropsychological training to administer and which has been shown to have good

test-retest reliability (Jones et al., 2016) - shows promise in being used clinically to detect and monitor early cognitive changes in MS. This study demonstrated that changes in vigilance and executive control attention network performance on the DalCAB can be detected in individuals with MS who are not classified as having cognitive impairments on the BICAMS, even after accounting for baseline RT differences between groups. In addition to differences in attention network performance, the DalCAB captured differences in sensorimotor speed (i.e., baseline RT) between groups. Baseline RT on the DalCAB was shown to differ between persons with MS not impaired on standard neuropsychological tests and the control group. Assessment tools that allow for the detection of subtle cognitive changes may allow for further understanding in the variability of MS prognoses and treatment outcomes.

The current analyses further validate the value of ISD as a measure of IIV in persons with MS (Wojtowicz et al., 2012). Differences in ISD between MS and control groups mirrored the differences in attention network performance between MS and control groups on the DalCAB, and differences in ISD were also observed in persons with MS who were not impaired on the BICAMS. This measure can be calculated from any computerized task that measures response speed over a number of trials, making it an easy addition to an existing testing protocol. Alternatively, it can be retroactively calculated from information in a computerized cognitive assessment research database. Previous work looking at ISD on computerized cognitive assessments in MS have used the Attention Network Test

- Interactions (ANT-I; Wojtowicz et al., 2013) and the Computerized Test of Information Processing (CTIP; Mazerolle et al., 2013; Wojtowicz et al., 2012).

As attention is a fundamental cognitive function that interacts with and affects other cognitive domains, such as memory (Chun & Turk-Browne, 2007), it is used frequently in day-to-day functioning. Subjective measures of self-reported cognitive deficits have shown poor associations with standard neuropsychological test tests, either under or over representing the prevalence of cognitive impairments (Gold, Schulz, Mönch, Schulz, & Heesen, 2003; Maor, Olmer, & Mozes, 2001). Computerized cognitive assessments, such as the DalCAB, may be able to more accurately capture deficits noticed by persons with MS in their real-world cognitive tasks. The current analyses were limited in that no tasks attempting to approximate real-world activities (e.g., sorting medications) were administered. Future research should include these tasks, given that reported real-world cognitive difficulties have been highlighted as a key priority for MS research (Sumowski et al., 2018). The DalCAB in its entirety requires 60 to 90 minutes to administer, which would likely hinder its use in MS clinics in the long term. Based on the current analyses and additional future work, the most useful DalCAB tasks for use in MS could be selected to reduce the total time required to administer the testing battery in a clinical setting. Although previous work has shown good test-retest reliability on the DalCAB in healthy young adults (Jones et al., 2016), and the current analyses suggest that the DalCAB could be used for detecting and monitoring cognitive changes over time in MS, longitudinal studies are needed to make this determination. Future longitudinal work should also include more

detailed information regarding disease modifying drugs taken by participants, to allow researchers to evaluate whether more detailed cognitive assessment measurement could contribute to understanding the variability in drug outcomes. This would provide a basis to determine whether the DalCAB should be trialed in larger drug studies as a cognitive tool to be used at baseline and as an endpoint.

Chapter 5. The Effect of Fatigue, Pain, Anxiety, and Depression on Attention Network Performance in Multiple Sclerosis

5.1 Background

Multiple sclerosis (MS) is a variable disease. Clinical symptoms differ considerably depending on the area of the CNS affected (Compston & Coles, 2008). Disease progression and severity vary between individuals and can be difficult to account for using white matter lesion volumes on MRI (Barkhof, 2002). Variability in cognitive deficits is equally difficult to account for, as measures of disease severity have had limited utility in explaining the variation in cognitive functioning in persons with MS (Amato et al., 2010; Ruggieri et al., 2003). Research continues to search for additional correlates of cognitive change and has turned to factors shown in other populations to affect cognitive functioning.

Depression and anxiety are common comorbid conditions in persons with MS and are more prevalent than in the general population. The global population with depression and anxiety is 4.4% and 3.6% respectively (World Health Organization, 2017), however, the prevalence of these conditions in population-based studies of MS ranges from 1.2% to 44.6% for anxiety and 4.98% to 58.9% for depression (Marrie et al., 2015a; Marrie et al., 2015b). Individuals living with depression and anxiety, but not MS, have been found to have higher rates of cognitive impairments. A meta-analysis of 24 studies found moderate deficits in executive functioning, memory, and attention in persons with major depressive disorder [based on either Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria or International Classification of Diseases criteria] compared to

healthy controls (Rock et al., 2014). A separate meta-analysis that also included studies examining anxiety disorders (based on DSM criteria), in adults aged 18 to 51, found that the pattern of cognitive impairments appeared to depend on the DSM subtype of anxiety disorder. For example, divided attention was reported to be affected in severe panic disorder but not executive functions, whereas social phobia was associated with executive function deficits (Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari, & Lönnqvist, 2008). A variety of tests were listed as having been used to assess “attentive and executive functions” in the studies included in this meta-analyses (p. 17): the Trail Making Test, the Wisconsin Card Sorting Task, the Stroop Color Word Interference Test, the Continuous Performance Test, the Paced Auditory Serial Addition Test, and the Controlled Oral Word Association Test. The effect of comorbid anxiety and depression has been examined in MS, however, studies vary as to whether cognition is affected and which cognitive domains are negatively influenced (DiGiuseppe et al., 2018; Leavitt et al., 2019; Whitehouse et al., 2019). The variability in how cognitive domains are conceptualized and assessed may contribute to the inconsistencies in this body of literature.

Pain and fatigue are also common symptoms in MS (Fiest et al., 2016b; O’Connor et al., 2008) that have potential associations with cognitive functioning. Studies of individuals with chronic pain have found symptoms of pain to be associated with decreased cognitive performance (see for review: Moriarty et al., 2011), however, there is limited work examining this association in persons with MS who experience pain. Newland and colleagues (2012) found that pain severity

was not associated with performance on a computerized measure considered to assess processing speed (the Paced Auditory Serial Addition Test) in a sample of 40 persons with MS, however, Motl and colleagues (2010) did find pain to be associated with perceived/subjective cognitive deficits in MS.

Many persons with MS report fatigue as having a significant impact on the cognitive functioning in everyday life (Fisk, Pontefract, et al., 1994; Hadjimichael et al., 2007). Although some authors have shown that increased symptoms of fatigue are associated with decreased cognitive performance (Amato et al., 2010; DiGiuseppe et al., 2018), others have found no association between the two (Deloire et al., 2005; Hulst et al., 2013). These studies varied in (1) the exact MS population studied, (2) how pain and fatigue were conceptualized, and also (3) which cognitive domains were assessed.

Hanken and colleagues (2015) systematically reviewed studies that examined fatigue and cognitive performance in MS, concluding that only the cognitive domains of vigilance and orienting consistently produced positive results (note: the authors used the term “alertness”, which corresponds to the orienting network described in the current thesis). The domains of memory, visuospatial abilities, language, working memory, and speed were reported to have either entirely negative (i.e., no association between fatigue and poor cognitive performance) or mixed results. It appears that further understanding of how attentional abilities interacts with symptoms of fatigue, pain, anxiety, and depression may contribute to understanding the variability in previous research on these symptoms and cognition.

Posner and Peterson's (1990) model of three attention networks provides a framework to examine attentional abilities broadly. Contrary to the conclusions of Hanken and colleagues (2015), previous work examining attention network performance using the Attention Network Test (ANT) in MS have largely found no association with depression and fatigue. Authors have shown that self-reported symptoms of depression (Crivelli et al., 2012; Urbanek et al., 2010) and fatigue (Urbanek et al., 2010) were not associated with attention network scores. Similarly, ISD on the ANT in an MS population was not found to be associated with depressive symptoms (Wojtowicz et al., 2013).

The aims of the analyses described in this chapter were to examine whether symptoms of fatigue, pain, anxiety, and depression accounted for variation in (1) attention network performance as measured by the DalCAB and (2) ISD in a sample of persons with MS with relatively low neurologic disability based on EDSS. Before addressing these aims, descriptive statistics of the variables of interest (i.e., fatigue, pain, anxiety, and depression) were calculated between groups (*5.2.1 Descriptive Statistics and Between Group Comparisons*) and the prevalence of clinically significant levels of depression and anxiety symptoms were calculated (*5.2.2 Prevalence of Clinically Significant Anxiety and Depression*), in order to capture the frequency and severity of these symptoms in the current MS sample. To address aim (1), regression models were used to evaluate whether self-reported symptoms of fatigue, pain, anxiety, and depression explained significant variability in attention network performance on the DalCAB (*5.2.3 Effect of Fatigue, Pain, Anxiety, Depression on Attention Network Performance in MS*).

Subsequently, to address aim (2), the same analyses were run to assess if these self-reported symptoms explained significant variability in measures of ISD (*5.2.4 Effect of Fatigue, Pain, Anxiety, Depression on Individual Standard Deviation*).

With the substantial variability in previous literature on the effects of fatigue, pain, anxiety, and depression on cognitive functioning in MS, it was difficult to specify hypotheses for the current chapter. Given this study is the first to use the DalCAB in a MS population, and the DalCAB produces novel composite measures of attention network performance, these analyses should be considered exploratory.

5.2 Data Analyses and Results

5.2.1 Descriptive Statistics and Between Group Comparisons

Descriptive statistics for self-reported symptoms of fatigue, pain, anxiety, and depression are listed in Table 17. In order to compare symptoms of pain and fatigue between the MS and control groups, independent samples t-tests (equal variances not assumed) were used. As control participants were excluded from the current study based on having received treatment or a diagnosis of anxiety or depression, symptoms of anxiety and depression were not compared between groups.

Table 17. Descriptive Statistics for Self-Reported Symptoms.

Self-Reported Factors	MS Group	Control Group	P-value*
Fatigue			
Impact of Fatigue *(FIS total score)*	47.57 (35.64)	16.63 (18.60)	< .001
Pain			
Impact of pain *(MOS-PES total score)*	11.17 (4.72)	8.98 (3.22)	.002
HADS			
Symptoms of Anxiety *(HADS-A Total Score)*	7.38 (4.40)	4.77 (3.13)	- - -
Symptoms of Depression *(HADS-D Total Score)*	4.10 (3.31)	1.65 (2.13)	- - -

Note. Mean (SD); *Independent samples t-test, equal variances not assumed; FIS = Fatigue Impact Scale, MOS-PES = Medical Outcomes Study – Pain Effects Scale, HADS = Hospital Anxiety and Depression Scale.

5.2.2 Prevalence of Clinically Significant Anxiety and Depression

As described in *Chapter 2, Method* (*2.2.3 Self-Report Questionnaires*), MS participants were classified as having clinically significant anxiety and/or depression using the MS-specific cut-off scores of 9 and 8 on the HADS-A and HADS-D, respectively (Honarmand & Feinstein, 2009; Marrie et al., 2018). In the MS group, 38.5% (*n* = 40) met criteria for clinically significant symptoms of anxiety and 14.4% (*n* = 15) met criteria for clinically significant symptoms of depression.

5.2.3 Effect of Fatigue, Pain, Anxiety, Depression on Attention Network Performance in MS

The subsequent analyses were run using the MS group only to examine the effects of fatigue, pain, anxiety, and depressive symptoms on measures of attention network performance in this MS group. As the control group was selected to be individuals with “normal” cognitive functioning, they do not represent the

general population in regard to the variables of interest in these analyses (e.g., individuals diagnoses of anxiety/depression were excluded, comorbid conditions that may be accompanied by pain or fatigue were excluded).

Regression models were used to examine whether self-reported symptoms of (1) fatigue, (2) pain, (3) anxiety, and (4) depression explained variance in attention network performance, as measured by the DalCAB. Each of the 9 DalCAB variables were entered individually as dependent variables, with each of self-report symptoms entered individually as independent variables. This resulted in 36 regression analyses (i.e., 9 DalCAB variables x 4 self-reported symptoms).

As described in *Chapter 3.2.6 (Accounting for Slowed Reaction Time in MS on the DalCAB)*, linear regression was used to parse out variation in DalCAB measures due to baseline RT differences between groups (Simple RT Task – Mean RT), leaving unstandardized residual DalCAB scores. These unstandardized residual scores were used in all DalCAB analyses described below. As an exception, the Go-No-Go Task – 20% Go Percent False Alarm variable was used without removing variation due to RT, as it is a variable based on accuracy not speed.

Symptoms of fatigue, pain, anxiety, and depression did not account for significant variability in any of the 9 DalCAB variables representing attention network performance. See Supplementary Table 4 for all regression results.

Four more regression models were used to examine whether self-reported symptoms of (1) fatigue, (2) pain, (3) anxiety, and (4) depression explained variance in baseline RT (i.e., Simple RT Task – Mean RT). Simple RT Task – Mean

RT was entered as the dependent variable in each of the four models with each of self-report symptoms entered individually as independent variables. Self-reported symptoms of fatigue [$F(1,102) = 9.680$, $p = 0.002$], pain [$F(1,102) = 6.844$, $p = 0.010$], and depression [$F(1,102) = 6.683$, $p = 0.011$] explained significant variability in Simple RT – Mean RT. Symptoms of anxiety did not explain significant variability [$F(1,102) = .023$, $p = 0.880$].

5.2.4 Effect of Fatigue, Pain, Anxiety, Depression on Individual Standard Deviation

Regression models were used to examine whether self-reported symptoms of (1) fatigue, (2) pain, (3) anxiety, and (4) depression explained significant variance in ISD. Each of the 6 ISD variables were entered individually as dependent variables, with each of self-report symptoms entered individually as independent variables. This resulted in 24 regression analyses (i.e., 6 ISD variables x 4 self-reported symptoms).

See Table 18 for all regression results. Self-reported symptoms of fatigue and pain explained significant variability in ISD for all tasks except Dual Task – ISD and Visual Search Task Conjunction Search – ISD. Self-reported symptoms of depression explained significant variability in Simple RT Task – ISD and Visual Search Task Feature Search – ISD.

Table 18. Variance in ISD Accounted for by Self-Reported Symptoms in MS Group.

ISD Variable	Fatigue	Pain	Anxiety	Depression
Simple RT – ISD	$F(1,102) = 7.087$, $p = .009$	$F(1,102) = 6.792$, $p = .011$	$F(1,102) = .127$, $p = .722$	$F(1,102) = 5.595$, $p = .020$
Choice RT – ISD	$F(1,102) = 10.566$, $p = .002$	$F(1,102) = 9.385$, $p = .003$	$F(1,102) = .227$, $p = .635$	$F(1,102) = 3.335$, $p = .071$
Dual Task – ISD	$F(1,98) = 1.656$, $p = .201$	$F(1,98) = .182$, $p = .671$	$F(1,98) = .032$, $p = .859$	$F(1,98) = .502$, $p = .480$
Vertical Flanker – ISD	$F(1,102) = 7.159$, $p = .009$	$F(1,102) = 7.997$, $p = .006$	$F(1,102) = .022$, $p = .881$	$F(1,102) = 1.257$, $p = .265$
Visual Search Feature – ISD	$F(1,102) = 5.944$, $p = .016$	$F(1,102) = 4.605$, $p = .034$	$F(1,102) = .027$, $p = .871$	$F(1,102) = 5.921$, $p = .017$
Visual Search Conjunction – ISD	$F(1,102) = 1.841$, $p = .178$	$F(1,102) = 3.792$, $p = .054$	$F(1,102) = .012$, $p = .913$	$F(1,102) = .575$, $p = .450$

Note. All 10 significant values were subject to a Benjamini-Hochberg correction for multiple comparisons and remained significant. Significant values are shaded.

5.3 Discussion

The analyses described in this chapter examined whether self-reported symptoms of fatigue, pain, anxiety, and depression accounted for variation in attention network performance and individual standard deviation (ISD) in persons with MS.

5.3.1 Effect of Fatigue, Pain, Anxiety, Depression on Attention Network Performance

As the control group was curated to not include factors known to affect cognition in the general public, such as having been diagnosed or treated for depression or anxiety, this chapter focused on the MS group only. Self-reported

symptoms of fatigue, pain, anxiety, and depression did not explain significant variability in attention network performance. Yet, symptoms of fatigue, pain, and depression did explain variability in baseline RT. Various authors have found that symptoms of depression are associated with or account for variance in cognitive functioning in MS when using standard neuropsychological tests (Benito-Leon, Morales, & Rivera-Navarro, 2002; Cutajar et al., 2000; Morrow et al., 2016). Anxiety has been less frequently examined despite being nearly as common as depression in the general population (4.4% versus 3.6%; World Health Organization, 2017) and in MS (21.9% vs 23.7%; Marrie et al., 2015b), however, a number of recent studies have shown that symptoms of anxiety affect cognitive functioning in MS when using standard neuropsychological tests (Morrow et al., 2016; Ribbons, Lea, Schofield, & Lechner-Scott, 2017; Whitehouse et al., 2019). Analyses using RT tasks have typically found that symptoms of depression were not associated with simple or choice RT task performance (Reicker et al., 2007; Stoquart-ElSankari et al., 2010), Sternberg task performance (Archibald & Fisk, 2000), or attention network performance as measured by the ANT (Crivelli et al., 2012; Urbanek et al., 2010). Symptoms of anxiety were not found to affect simple or choice RT task performance in persons with MS (Stoquart-ElSankari et al., 2010). In this regard, the findings of the current study of attention network performance on the DalCAB are consistent with other studies that examined effects of anxiety and depression symptoms on RT-based tasks.

However, Lubrini and colleagues (2016) examined performance on RT tasks between persons with MS diagnosed with depression (based on the DSM-

5) and persons with MS who were not. Persons with MS and depression were significantly slower on a choice RT task and a choice RT search task (i.e., make a yes/no determination as to whether a target letter appeared in strings of six letters). Others have shown that the effects of depression and anxiety on cognition in MS vary depending on whether self-reported symptoms or diagnoses of depression/anxiety were examined; Whitehouse and colleagues (2019) found current symptoms of anxiety to explain unique variance in tests associated with processing speed, verbal learning, and working memory, and symptoms of depression to explain unique variance on a test associated with processing speed. Although meeting criteria for anxiety disorder continued to explain variance in processing speed (but no longer verbal learning and working memory), major depressive disorder was not associated with cognitive functioning.

Self-report symptoms of fatigue have been shown to be associated with symptoms of anxiety and depression in work by others (Berrigan et al., 2016; Leavitt et al., 2019; Morrow et al., 2016). The literature regarding associations between fatigue and cognitive functioning in MS has been mixed, with some studies finding associations (Amato et al., 2010; DiGiuseppe et al., 2018; Ruano et al., 2017) and others not (Deloire et al., 2005; Hulst et al., 2013), when using standard neuropsychological tests as measures of cognition. Yet studies that used RT-based tasks to measure cognitive functioning in MS did not find symptoms of fatigue to impact RT on a Sternberg task (Archibald & Fisk, 2000) or attention network performance scores on the ANT (Urbanek et al., 2010).

As there has been limited previous work examining the effect of pain on cognitive functioning in MS, the current results should be considered with some caution. In the current study, self-reported symptoms of pain did not explain variability in attention network performance, although pain did account for variability in baseline RT (i.e., Simple RT Task – Mean RT). Newland and colleagues (2012) examined the effect of pain severity in MS on a test commonly attributed to information processing speed (the Paced Auditory Serial Addition Task) and found no association. However, persons with MS do report their pain to be associated with subjective/perceived level of cognitive deficits (Motl et al., 2010) and studies of on individuals with chronic pain have found symptoms of pain to be associated with decreased cognitive performance (see for review: Moriarty et al., 2011). The current sample included participants with relapsing-remitting MS and low neurologic disability based on EDSS, and would be anticipated based on previous work to experience lower levels of pain-related disability than more severely affected MS groups, such as those with secondary progressive or primary progressive MS (Fiest et al., 2015). Persons with different subtypes of MS may endorse more pain [based on work by Fiest and colleagues (2015)] or perhaps individuals with more neurologic disability may endorse more pain, which may impact their cognitive functioning.

5.3.2 Effect of Fatigue, Pain, Anxiety, Depression on Individual Standard Deviation

Self-reported symptoms of depression, fatigue, and pain did explain variability in ISD on some tasks in the MS group, though symptoms of anxiety did

not. Previous work on ISD in MS has not found depressive symptoms to be associated with ISD (Wojtowicz et al., 2013), however, the authors were looking at ISD of performance across all trials of the Attention Network Test – Interactions and did not divide ISD by task, as was done in the current study. Bunce, Handley, and Gaines (2008) examined age, symptoms of depression and anxiety, and ISD in a sample of 300 adults aged 18 to 85. The authors did not find symptoms of depression or anxiety to have a significant relationship with ISD on computerized simple or choice RT tasks, a visual search task, or executive control tasks. However, a significant age and symptom interaction was found with the visual search tasks whereby in the sample with high depression and anxiety, older individuals had greater ISD than younger individuals, yet this age discrepancy was not observed in those with low depression and anxiety. This interaction suggests that the combination of both depression and/or anxiety and increased age contributes to increased ISD. Relationships between ISD, fatigue, and pain have not been examined previously in MS. Studies on self-reported symptoms of fatigue and pain have had mixed results in showing a relationship of these symptoms to objective cognitive performance, as discussed in the previous section. As ISD appears to be associated with these symptoms, it could be used to objectively demonstrate cognitive changes related to these MS symptoms.

In summary, self-reported symptoms of fatigue, pain, anxiety, and depression did not account for variability in attention network performance in the current analyses, however, fatigue, pain, and depression did account for variability in baseline RT (aim 1). Symptoms of fatigue, pain, and depression also accounted

for variability in measures of ISD, specifically on the Simple RT Task, Choice RT Task, Vertical Flanker Task, and Visual Search Task Feature Search (aim 2).

5.3.3 Implications, Limitations, and Future Research

The current analyses have shown that attention network performance on the DalCAB is not affected by common self-reported symptoms in MS. Performance on standard neuropsychological tests have been shown by some to partly reflect the presence and/or severity of some of these symptoms. If the DalCAB is a measure of cognitive functioning unaffected by these common symptoms, this is promising with regard to the utility of the DalCAB in a MS clinic setting. ISD does appear to be affected by these symptoms, however, this may be useful in capturing objective cognitive changes in individuals who report an adverse impact of their symptoms of fatigue, depression, and pain on their cognitive functioning.

Although depression did not explain variability in attention network performance, only 14.4% of the MS sample endorsed clinically significant levels of depressive symptoms. Different results may have occurred if there were higher levels of depression in the sample, however, the sample is likely representative of persons with MS with low neurologic disability based on EDSS. The self-report questionnaire selected to measure the impact of pain in the current sample [i.e., the Medical Outcomes Study – Pain Effects Scale (MOS-PES)] was chosen given that it was created specifically for persons with MS, however, it was in retrospect a limiting choice. The MOS-PES does not have the psychometric data and information regarding a clinically meaningful score necessary to appropriately

interpret the results of the current analyses. Given that limited previous literature exists on the effects of pain on cognitive functioning in MS, more comprehensive measurement of pain is needed in future studies on cognition in order to explore this potential association.

Chapter 6. MRI Sub-Study: Examining Associations Between Structural Brain Changes and Attention Network Performance in Multiple Sclerosis

6.1 Background

Magnetic resonance imaging (MRI) has become the primary diagnostic tool for MS (Thompson et al., 2018) and continues to be used in clinical practice to identify and monitor the development of white matter lesions. Yet work attempting to draw connections between the volume of white matter lesions and level of neurologic disability has been variable. The term “clinical-radiological paradox” has been used to describe the weak association between severity of clinical disability and volume of white matter lesions imaged using MRI (Barkhof, 2002).

Although MS has long been considered a white matter disease (McKhann, 1982), grey matter involvement has been increasingly recognized. Studies have found that measures which consider both white and grey matter volume, such as normalized brain volume or brain parenchymal fraction (BPF), have shown decreased brain volume or BPF for persons with MS who are cognitively impaired (Hulst et al., 2013; Zivadinov et al., 2001b; Zivadinov et al., 2001a). Deep grey matter volumes, specifically, have shown promising associations with cognitive functioning in MS. Among the deep grey matter structures, the thalamus, caudate, putamen, and hippocampus have been recognized as relevant structures to cognition in this population (Batista et al., 2012; Benedict et al., 2009; Bisecco et al., 2018; Eijlers et al., 2019; Pravatà et al., 2017). Yet the combination of associated structures and cognitive processes affected varies between studies.

For example, Batista and colleagues (2012) found that thalamus and putamen volume predicted information processing speed performance (on the Symbol Digit Modalities Test and Paced Auditory Serial Addition Test), whereas Benedict and colleagues (2009) found the thalamus and caudate to have the strongest correlations with a test of information processing speed (the Symbol Digit Modalities Test).

Limitations in the methods used to assess cognitive impairments in MS may contribute to the inconsistencies in correlates with neuroimaging measures in MS. As discussed previously, many cognitive tasks are commonly purported to assess one cognitive domain despite requiring a variety of cognitive abilities to complete. This lack of precision in assessing cognitive functions becomes particularly problematic when attempting to associate a specific cognitive deficit with specific CNS damage. Petersen and Posner's (2012) most recent review of their model of three attention networks provides a basis for studying correlates between neuroanatomical changes on MRI and changes in attentional abilities. Their three networks have been shown to function within the following neuroanatomical areas: (1) orienting – appears to function largely within the parietal cortex with connections to frontal areas such as the frontal eye fields and ventral frontal cortex, (2) vigilance – appears to rely on brain stem arousal, such as norepinephrine release from the locus coeruleus, and systems within the right cerebral cortex, (3) executive control – appears to operate within the lateral frontal and parietal regions (the frontoparietal component of the network), and the medial frontal/cingulate cortex and anterior insula (the cinguloopercular component of the network).

A previous assessment tool for measuring these three attention networks, the ANT, has been criticized for its psychometric properties in the general population (MacLeod et al., 2010) and has been shown to provide inconsistent results depending how the network scores were calculated in MS populations (Roth et al., 2015). In addition, the ANT provides only one score per attention network; Recent recommendations by Sumowski and colleagues (2018) for priorities for the field of cognition in MS, suggest that future research should move away from using one cognitive test or measure to represent a cognitive domain, and should consider latent variables “as purer measures of targeted functions” (p. 2). The DalCAB, which produces multiple scores associated with each attention network, provides a promising assessment tool for future work examining attention networks in relation to specific pathological processes in MS.

In addition, a computerized measure such as the DalCAB allows for the calculation of individual standard deviation (ISD), which is considered to be a behavioural measure of CNS integrity (MacDonald et al., 2006). In an MS population specifically, ISD has been shown to be associated with white matter structural integrity, as ISD on a simple RT task was associated with functional connectivity across more white matter fibre tracks than mean-RT on the same task (Mazerolle et al., 2013). ISD has been shown to differ between MS and control groups, even when the overall slowed RT of persons with MS is considered (Wojtowicz et al., 2012; Wojtowicz et al., 2013).

The aims of the analyses described in this sub-study were to examine whether MRI measures of brain structure and damage, that have commonly been

examined in studies of cognition in persons with MS, were associated with (1) attention network performance as measured by the DalCAB or (2) ISD on the DalCAB tasks. Before addressing these aims, the BPF was calculated (*6.3.1 Calculating Brain Parenchymal Fraction*) and descriptive statistics of the variables of interest were compared between groups (*6.3.2 Descriptive Statistics of Structural MRI Measures*). The structural MRI variables of interest were BPF, white matter lesion volume, grey matter lesion volume, hippocampus volume, thalamus volume, caudate volume, and putamen volume. To address aim (1), correlations were used to explore whether structural MRI measures were associated with attention network performance on the DalCAB (*6.3.3 Associations Between Structural MRI Measures and Attention Network Performance*). To address aim (2), correlations were used to explore whether structural MRI measures were associated with ISD on the DalCAB tasks (*6.3.4 Associations Between Structural MRI Measures and Individual Standard Deviation*). For completeness of the chapter and comparison to previous literature, correlations were also used to explore whether structural MRI measures were associated with standard neuropsychological test scores (*6.3.5 Associations Between Structural MRI Measures and Standard Neuropsychological Test Scores*) and clinical characteristics (*6.3.6 Associations Between Structural MRI Measures and Clinical Characteristics*).

Given this study was the first to use the DalCAB in a MS population, and the DalCAB produces novel composite measures of attention network performance, these analyses should be considered exploratory. However,

structural MRI measures were selected based on previous work showing these measures to be relevant to cognitive functioning in MS. Cognitive functioning in previous studies has been measured using standard neuropsychological tests or other computerized measures, and the individual studies vary in the combinations of brain structures and cognitive domains in which associations have been reported.

6.2 MRI Method

6.2.1 MRI Sub-study Participants

Participants who completed the behavioural data collection, outlined in *Chapter 2 (Method)*, were asked if they would be willing to participate in an additional MRI sub-study. The only additional criteria for participation in the MRI sub-study were that (1) participants could not have any contraindications to receiving an MRI scan (e.g., metal implants, fixed piercings, etc) and (2) participants had to be available to receive the MRI scan within six weeks of completing their behavioural data collection. All MRI participants completed a screening form, followed by questions from an MRI technician, to confirm they had no contraindications to receiving an MRI scan before entering the scanner. Participants were compensated for the cost of their parking at the hospital. See Figure 5 for flow of included and excluded participants in the MRI sub-study.

MS Group.

Forty-two MS participants received MRI scans as part of the sub-study. However, three of these participants were among those whose data were withdrawn from the study or excluded from the analyses, as described in *Chapter*

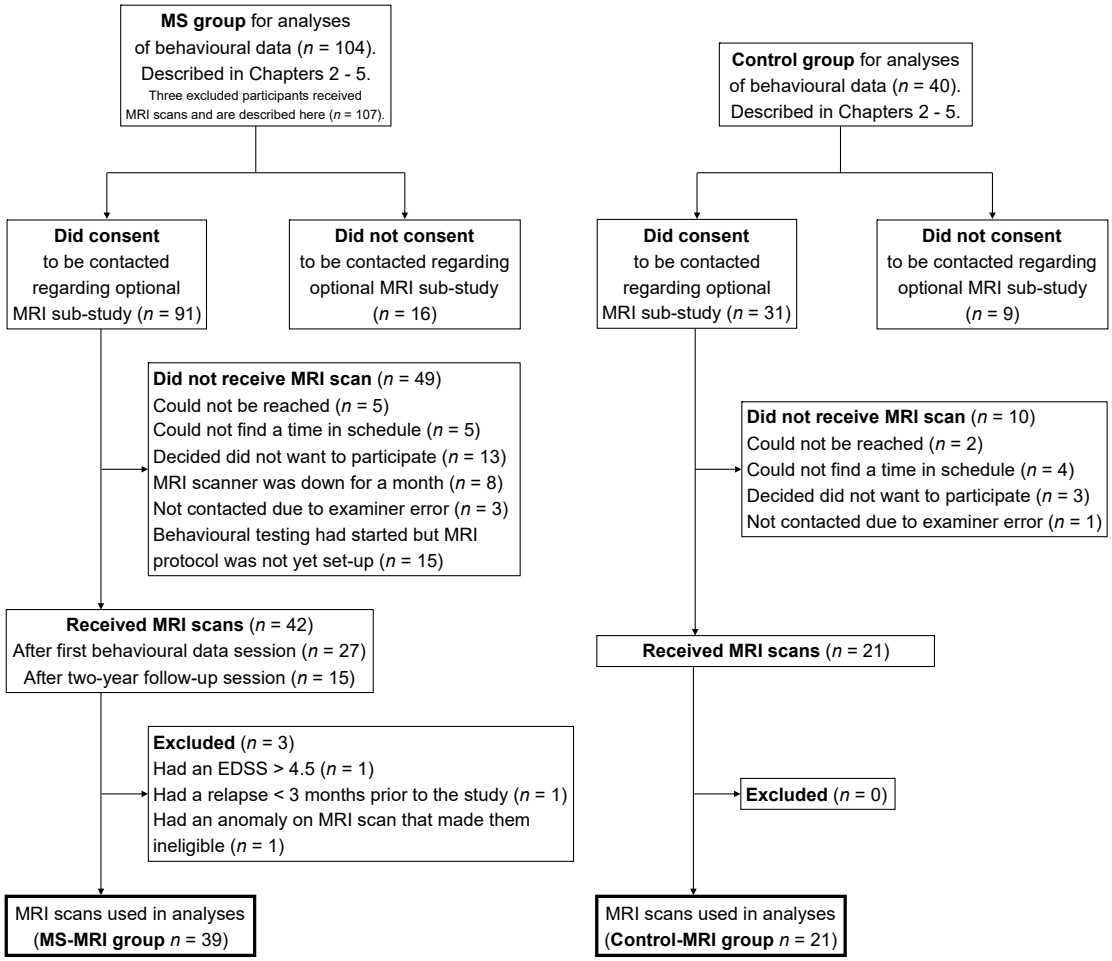
2 (Method). The remaining 39 participants were mainly female (82.1%), spanning almost the full range of recruited ages (21 to 60 years of age; *M* = 46.6 years) and levels of education (12-19 years; *M* = 14.7 years). EDSS scores ranged from 0 to 4.5 and the majority (82.1%) had EDSS scores of 2.5 or less (*M* = 1.8; *Interquartile range* = 1.5 - 2.5). These 39 participants are referred to as the "MS-MRI group".

For 15 of the 39 participants in the MS-MRI group, their MRI and behavioural measures were collected two years after they had completed the initial study. This two-year follow-up assessment, using the behavioural measures, had been planned as part of the overall program of research. However, as reassessment data were only available for a few of the initial study participants, no analyses comparing the initial and reassessment behavioural data were included in the current thesis. Prior to receiving their MRI, these 15 participants were re-screened to ensure they still met the original criteria for study enrollment. See *Chapter 2.1 (Participants – MS Group)* for complete description of study enrollment criteria. For these 15 participants, behavioural data from their second assessment were used for MRI-related analyses. Five of the 15 participants had not had their EDSS evaluated at their most recent appointment at the Dalhousie MS Research Unit and their neurologic disability was estimated using the Patient Determined Disease Steps (PDDS) as a proxy for EDSS score. The PDDS is a validated patient-reported disability measure that is highly correlated with a physician-determined EDSS score (r_s = 0.958) on neurologic examination (Hohol, Orav, & Weiner, 1995).

Control Group.

Twenty-one control participants received MRI scans. The participants were mainly female (90.5%), ranging from 24 to 60 years of age (M = 48.6), with 12 to 16 years of education (M = 15.0). They did not differ from the MS-MRI group in terms of age [t(39.6) = -0.711, p = 0.481] or years of education [t(54.7) = -0.773, p = 0.443] using independent sample's t-tests (equal variances not assumed). The groups also did not differ in terms of their percentage of female participants [X^2(1) = 0.760, p = 0.383] using Pearson Chi-Squared. These 21 control participants are referred to as the "control-MRI group".

Figure 5. Flow of Included and Excluded Participants in the MRI Group.



6.2.2 MRI Procedure

The MRI processing procedure (i.e., MRI Acquisition, MRI Conversion and Defacing, MRI Preprocessing, MRI Analyses) was designed by Carl Helmick, B.C.S., manager of the Brain Imaging Laboratory, Department of Psychiatry, Dalhousie University (Nova Scotia, Canada). Simplified descriptions of the conversion, defacing, preprocessing, and analyses procedures are described below and the detailed MRI pre-processing and analysis "pipeline" (provided by Carl Helmick) is included in Appendix B.

MRI Acquisition.

MRI scans were performed on a 3.0 Tesla scanner (GE MR750; GE Healthcare, Waukesha, Wisconsin) fitted with a 32-channel RF-coil (Invivo Corp, Gainesville, Florida). The following three anatomical scans were acquired in sagittal plane as 3D sequences with whole-head coverage: T1-weighted fast spoiled gradient recalled echo (FSPGR) sequence [echo time (TE)/repetition time (TR) = 4.0/1.33ms, flip angle = 9°, inversion time (TI) 450ms, number of excitations = 2], T2-weighted CUBE sequence (TE/TR = 2500/100ms, flip angle = variable, number of excitations = 1), and a T2-weighted fluid-attenuated inversion recovery (FLAIR) CUBE sequence (TE/TR = 12000/101ms, flip angle = variable, number of excitations = 1). The following parameters were the same for all three sequences: matrix = 256 × 256, field of view (FOV) = 256mm, slice thickness/gap = 1.0/0.0mm, number of slices = 184. A three-plane localizer and calibration scan were run prior to beginning the scans of interest. Total acquisition time was 23 minutes and 24 seconds.

MRI Conversion and Defacing.

All MRI sequences produced by the scanner [(Digital Imaging and Communications in Medicine (DICOM) files] were converted into compressed 3D Neuroimaging Informatics Technology Initiative (NIFTI) image files using the image conversion tool “dcm2niix” (Li, Morgan, Ashburner, Smith, & Rorden, 2016). All three anatomical scans were defaced (structurally anonymized) to remove face, neck, and ear voxels. The defaced images were visually reviewed to ensure identifying features were properly removed, and that participant brain images were free of artifacts and anomalies.

MRI Preprocessing.

Each participant’s three structurally anonymized scans (i.e., T1, T2, and T2 FLAIR) were cropped to remove excess neck and empty slices outside the head. Bias (inhomogeneity) correction was applied using the FSL “FAST” program (Zhang, Brady, & Smith, 2001). Scans were aligned to Montreal Neurologic Institute (MNI)152 Template space [a brain template created from spatially-aligning and averaging the whole-brain scans of 152 healthy adults (Mazziotta et al., 2001)] using ACPC-alignment (i.e., where the anterior commissure and the posterior commissure are horizontally aligned on same slice). However, prior to conducting ACPC-alignment, a more accurate skull-stripped brain image was created by linearly and nonlinearly registering the cropped and bias-corrected T1-weighted image to the MNI152 Template. Then, this T1-weighted image was linearly registered to the MNI152 Template.

After completing these preprocessing steps on the T1-weighted images, the T2-weighted and T2-weighted FLAIR images were bias-corrected and co-registered to the ACPC-aligned T1-weighted image with a rigid-body linear registration (using the FSL "FLIRT" program; Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001).

MRI Analyses.

Automated lesion segmentation was conducted using the Lesion Segmentation Toolbox (LST) to estimate the volume of lesioned tissue for each participant. The T1-weighted and T2-weighted FLAIR images were input into the LST, and a lesion mask was generated using the Lesion Growth Algorithm (Schmidt et al., 2012). FSL lesion-filling tool was used to replace lesion-labelled voxels on the T1-weighted image with normal-appearing white-matter voxel intensity values. Neuroimaging tools used to estimate total brain volume and subcortical structures have difficulty performing their operations on MS brains, given the dispersed lesions. MS lesions often appear as “black-holes” on a T1-weighted image and without lesion-filling, will often be misclassified during tissue segmentation as gray matter or cerebrospinal fluid instead of white matter.

Tissue segmentation was completed on the lesion-filled T1-weighted brain by using the FSL “FAST” program (Zhang et al., 2001). This produced lesion-filled volume estimates of white matter, grey matter, and cerebrospinal fluid.

Final linear 12-Degrees of Freedom and non-linear registrations to the MNI152 Template were calculated using the cropped, bias-corrected, ACPC-aligned T1-weighted brain image. These final registrations were conducted with

the lesion-mask included, as the presence of lesions in a MS brain creates registration failures or incorrect registration results to the MNI152 Template. A MNI152 brain scalar value was derived from the final transformation, representing the degree of physical scaling required to spatially normalize each subject brain to the MNI152 template. Subcortical structure segmentation was performed using the FSL “FIRST” program (Patenaude, Smith, Kennedy, & Jenkinson, 2011) on the lesion-filled T1-weighted image to estimate volume values of the thalamus, hippocampus, putamen, and caudate.

The following anatomical volumetric measures were derived: estimated total brain volume, estimated white matter volume, estimated grey matter volume, cerebral spinal fluid volume, estimated thalamus volume, estimated hippocampus volume, estimated putamen volume, estimated caudate volume, lesion volume, volume of lesion overlap with each tissue type and structure (e.g., lesion overlap in white matter), and the MNI152 brain scalar value. As estimated volume values were calculated using participant’s lesion-filled T1-weighted image, lesion overlap values were subsequently subtracted from their corresponding estimated volume value to give the true volume estimates.

Prior to conducting group analyses involving volume, volume values were multiplied by each individual’s MNI152 brain scalar value in order to scale volumes into MNI152 space. This scaling process allowed for direct volume comparisons between individuals by adjusting for individual brain size.

6.3 Statistical Data Analyses and Results

6.3.1 Calculating Brain Parenchymal Fraction

Brain Parenchymal Fraction (BPF), a measure of whole brain atrophy, was calculated using the following formula outlined by Rajagopalan and Pioro (2015): [(Volume of grey matter + white matter)/(Volume of grey matter + white matter + cerebral spinal fluid)] x 100. The volume values used in this calculation were the original estimated volume values, prior to subtracting lesioned tissue, so to reflect only atrophy and not discount demyelinated tissue.

6.3.2 Descriptive Statistics of Structural MRI Measures

Participants completed their MRI scan 4.0 weeks, on average, following their behavioural testing session (*SD* = 1.2 weeks, range: 1.2 to 6.4 weeks). Although the aim was to have all MRIs completed within 6 weeks of participant's behavioural testing, 1 participant received their MRI scan 6 weeks and 3 days post-behavioural testing.

See Table 19 for descriptive statistics of all structural MRI measures compared between the MS-MRI and control-MRI groups. As expected, MS participants had significantly greater white and grey matter lesion volumes. MS participants had lower hippocampus volume, thalamus volume, caudate volume, and putamen volume than controls, however, BPF did not differ between groups.

Table 19. Descriptive Statistics for Structural MRI Measures.

Structural MRI Measures	MS-MRI Group	Control-MRI Group	*p*-value
N	39	21	
BPF	78.8 (3.0)	79.9 (2.0)	.078
White matter lesion volume	6695.5 (8718.8)	435.0 (931.5)	< .001
Grey matter lesion volume	489.9 (762.5)	84.6 (166.2)	.003
Hippocampus volume	9628.2 (1120.7)	10251.4 (616.9)	.007
Thalamus volume	19743.2 (2165.5)	21281.0 (1243.5)	.001
Caudate volume	8698.9 (1212.4)	9311.1 (817.1)	.024
Putamen volume	11961.2 (1694.3)	13288.8 (1000.0)	<.001

Note. Mean (SD); All volume values are in mm^3; BPF = brain parenchymal fraction; P-values from independent samples t-test, equal variances not assumed; Significant values are shaded. All 6 significant t-tests were jointly subjected to the Benjamini-Hochberg correction for multiple comparisons and remained significant.

6.3.3 Associations Between Structural MRI Measures and Attention Network Performance

To address aim (1) of this chapter, Spearman non-parametric correlations (two-tailed) were used to explore associations between structural MRI measures and attention network performance as measured by the DalCAB. Given the majority of structural MRI measures were shown to differ between MS and control groups in this sample (see *Chapter 6.3.2 Descriptive Statistics of Structural MRI Measures*, above), the correlations were run on the MS sample only. This allows for examining whether associations between structural MRI measures and attention network performance exist within an MS sample.

As described in *Chapter 3.2.6 (Accounting for Slowed RT in MS on the DalCAB)*, linear regression was used to parse out the variation in DalCAB measures accounted for by baseline RT differences between groups (Simple RT Task – Mean RT), leaving unstandardized residual DalCAB scores. These unstandardized residual scores were used in all correlational analyses involving these DalCAB measures.

See Table 20 for correlations between the structural MRI measures and attention network performance as measured by the DalCAB, in the MS group only. Simple RT Task – Mean RT was correlated with all structural MRI measures except hippocampus volume, however, none of the attention network measures were correlated with the structural MRI measures examined.

Table 20. Correlations Between Structural MRI Measures and Attention Network Performance in the MS Group.

DalCAB Measures *(Across)* / **Structural MRI Measures** *(Below)*	Simple RT	Vigilance Network			Orienting Network		Executive Control Network			
		VS Feature search mean RT	DT switch-cost	CRT standard deviation	VS Conjunction search mean RT	VS Conjunction search set size effect	GNG 20% go percent false alarm	IM mean RT	IM target absent effect	DT cost
BPF	-.350	-.221	-.102	.052	-.303	-.162	-.292	-.264	-.161	-.171
White matter lesion volume	.469	-.062	-.080	-.095	.086	-.027	.058	.034	-.056	-.013
Grey matter lesion volume	.495	-.048	.097	-.090	.036	-.056	.152	.101	.007	.062
Hippocampus volume	-.199	-.057	-.068	-.037	-.070	.008	-.166	-.148	-.109	.139
Thalamus volume	-.472	-.117	-.165	-.020	-.119	-.014	-.108	-.064	-.040	-.176
Caudate volume	-.481	-.107	-.034	-.132	.114	.145	.093	-.073	-.063	.045
Putamen volume	-.317	-.127	.166	.116	-.058	.025	.108	.009	.065	.142

Note. Spearman non-parametric correlations; DalCAB variables relating to the attention networks have the variance attributed to Simple RT Task – Mean RT parceled out; All 6 significant correlations were subject to a Benjamini-Hochberg correction and remained significant. Significant correlations are shaded.

6.3.4 Associations Between Structural MRI Measures and Individual Standard Deviation

To address aim (2) of this chapter, Spearman non-parametric correlations (two-tailed) were used to explore associations between structural MRI measures and ISD on the DalCAB tasks. These correlations were run on the MS sample only.

See Table 21 for correlations between the structural MRI measures and ISD on the DalCAB tasks, in the MS group. White and grey matter lesion volume, hippocampus volume, and thalamus volume were associated only with Simple RT Task – ISD. Caudate volume was associated with Simple RT Task – ISD as well as Choice RT Task – ISD, Vertical Flanker Task – ISD, and Visual Search Task Feature Search – ISD. BPF was only associated with Visual Search Task Conjunction Search – ISD, and putamen volume was not associated with any ISD measures.

Table 21. Correlations Between Structural MRI and ISD in the MS Group.

Structural MRI Measures	ISD Measures					
	Simple RT	Choice RT	Dual Task	Vertical Flanker	Visual Search Feature	Visual Search Conjunction
BPF	-.251	-.097	-.317	-.233	-.191	-.330
White matter lesion volume	.452	.217	.202	.151	.299	.288
Grey matter lesion volume	.426	.226	.307	.217	.282	.242
Hippocampus volume	-.333	-.223	-.144	-.183	-.196	-.209
Thalamus volume	-.419	-.280	-.266	-.272	-.305	-.250
Caudate volume	-.439	-.413	-.161	-.321	-.409	.008
Putamen volume	-.268	-.080	-.019	-.042	-.225	-.045

Note. Shaded cells represent significant Spearman non-parametric correlations (two-tailed). All 9 significant correlations were jointly subjected to a Benjamini-Hochberg correction and remained significant.

6.3.5 Association Between Structural MRI Measures and Standard Neuropsychological Test Scores

For completeness of the chapter, Spearman non-parametric correlations (two-tailed) were used to explore associations between structural MRI measures and the standard neuropsychological tests scores that comprise the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS: SDMT Total, CVLT-II Total Immediate Recall, BVMT-R Total Immediate Recall) in the MS group.

SDMT Total and CVLT-II Total Immediate Recall were not associated with any structural MRI measures, while the BVMT-R Total Immediate Recall was associated with BPF as well as both white and grey matter lesion volumes.

Table 22. Correlations Between Structural MRI Measures and Standard Neuropsychological Tests that Comprise the BICAMS in the MS Group.

Structural MRI Measures	BICAMS Test Scores		
	SDMT Total	CVLT-II Total Immediate Recall	BVMT-R Total Immediate Recall
BPF	.261	-.040	.347
White matter lesion volume	-.194	-.016	-.328
Grey matter lesion volume	-.201	-.157	-.391
Hippocampus volume	.020	.141	.249
Thalamus volume	.144	.160	.288
Caudate volume	.193	.100	.179
Putamen volume	.274	-.156	.230

Note. Shaded cells represent significant Spearman non-parametric correlations (two-tailed). All 3 significant correlations were jointly subjected to a Benjamini-Hochberg correction and remained significant.

6.3.6 Associations Between Structural MRI Measures and Clinical Characteristics

Also for completeness of the chapter, Spearman non-parametric correlations (two-tailed) were used to explore associations between structural MRI measures, demographics (age, years of education), health-related quality of life (single attribute utility score on the HUI), and clinical characteristics (EDSS, years since onset). Years since diagnosis was not examined due to its high correlation with years since onset ($r_s = 0.945$, $p < 0.001$).

See Table 23 for correlations between the structural MRI measures and the MS participant characteristics. EDSS, years of education, and health-related quality of life as measured by the HUI were not correlated with any structural MRI measures. Years since MS onset was correlated with all MRI measures except

caudate and putamen volume. Age was correlated with BPF, grey matter lesion volume, and thalamus volume.

Table 23. Correlations between Structural MRI Measures and Participant Characteristics in the MS Group.

Structural MRI Measures	**Participant Characteristics**				
	EDSS	Years Since MS Onset	Age	Years of Education	HRQoL
BPF	-.284	-.493	-.360	.206	.181
White matter lesion volume	.240	.355	.222	-.095	.049
Grey matter lesion volume	.202	.557	.401	-.153	-.164
Hippocampus volume	-.090	-.432	-.064	.131	-.061
Thalamus volume	-.213	-.655	-.469	.267	.087
Caudate volume	-.031	-.153	-.243	.252	.126
Putamen volume	-.067	-.179	-.113	.187	-.201

Note. HRQoL = Health-related quality of life, represented by the HUI single attribute utility score; Shaded cells represent significant Spearman non-parametric correlations (two-tailed). All 8 significant correlations were jointly subjected to a Benjamini-Hochberg correction and remained significant.

6.4 Discussion

The analyses described in this chapter examined whether structural MRI measures were associated with attention network performance or individual standard deviation (ISD), as assessed by the Dalhousie Computerized Attention Battery (DalCAB), in persons with MS otherwise thought to have low neurologic disability based on the Extended Disability Status Scale (EDSS).

As expected, MS participants had more white matter lesion volumes compared to controls, however, MS participants also had more grey matter lesion volumes and decreased deep grey matter structure volumes (hippocampus,

thalamus, caudate, and putamen). This is consistent with the shift away from conceptualizing MS as solely a white matter disease.

The brain parenchymal fraction (BPF) was the only structural MRI measure to not differ between MS and control participants. BPF is a measure of whole-brain atrophy shown to be sensitive to small amounts of change in the MS brain over time in persons with low EDSS (e.g., EDSS 1.0 - 3.5; Rudick et al., 1999). A number of groups have shown BPF to differ between RRMS and control participants; Grassiot, Desgranges, Eustache, and Defer (2009) included eight studies in their systematic review of brain atrophy in MS, all of which showed decreased BPF compared to healthy controls. Among previous studies, there is variability in magnitude of BPF difference between MS and controls. This variability is seen even between studies with similar MS samples. For example, Sanfilipo and colleagues (2005) reported a 4.1% difference in BPF between controls and MS participants [MS group: 24 – 53 years of age, n = 35 relapsing-remitting (RR)MS, n = 6 secondary progressive (SP)MS, M_{EDSS} = 3.2]. Tiberio and colleagues (2005) reported a 2.8% difference at baseline in BPF between groups (MS group: 26 – 56 years of age, n = 21 RRMS, no SPMS, Med_{EDSS} = 1.0). The MS sample by Sanfilipo and colleagues (2005) did have a slightly higher EDSS than Tiberio and colleagues (2005) and included some SPMS participants, which could explain why Sanfilipo and colleagues (2005) reported a greater BPF difference (4.1% versus 2.8%). By comparison in the current study, the average BPF in the MS group was 1.4% less than the control group. It has also been speculated by Grassiot and colleagues (2009) that the difference in MRI slice size between the two example studies listed

above, 2.5mm (Sanfilipo et al., 2005) versus 1.5mm (Tiberio et al., 2005), may have attributed to this discrepancy, whereby the smaller slice size gave a more accurate estimate of BPF and therefore a smaller BPF value. The slice size in the current study was 1.0mm, and therefore, is likely an accurate estimate of the BPF in this sample of persons with MS.

6.4.1 Attention Network Performance and Structural MRI Measures

All structural MRI measures were correlated with baseline RT (Simple RT Task – Mean RT), however, no structural MRI measures were correlated with any measures of attention network performance. Omisade and colleagues (2012) found that RRMS participants with an abnormal MRI were significantly slower on all ANT-I tasks compared to MS participants with mild changes on MRI and healthy controls. Although the executive control network was also affected in the abnormal MRI group, in the current study there was no association between performance on the executive control network and structural MRI measures. Bonnet and colleagues (2010) examined performance on modified go-no-go tasks in relation to functional MRI connectivity in persons with RRMS. For the go-no-go task and a complex go-no-go task the MS participants recruited larger networks than controls, however, cerebral activation was not found to be correlated with lesion volume. These results suggest that although there may be differences in functioning on attention networks between MS and control participants, these differences in functioning may not be captured by MRI measures of brain structure and lesion volume.

6.4.2 Individual Standard Deviation on the DalCAB and Structural MRI Measures

Simple RT Task – ISD was correlated with five MRI measures, all except for putamen volume and BPF. No other ISD measure was associated broadly with the MRI measures. Of the five remaining ISD measures, four ISD measures were each correlated with one MRI measure, and one ISD measure was not correlated with any MRI measures. Of the ISD measures that differed between the MS and control groups in previous chapters, Simple RT Task – ISD had the smallest effect size (see *Chapter 4.2.3 Differences in Intra-Individual Variability Between Groups)*. The current analyses therefore suggests that even small changes in ISD on a simple RT task are associated with non-specific changes in neuroanatomy, consistent with ISD being a behavioural indicator of central nervous system (CNS) integrity (MacDonald et al., 2006).

Caudate volume was the only structural MRI measure associated with ISD on multiple DalCAB tasks: Simple RT Task, Choice RT Task, Vertical Flanker Task, and Visual Search Task Feature Search. This is in line with previous work in MS that found caudate volume to differ between cognitively impaired and cognitively intact persons with MS (Pravatà et al., 2017), and reported the caudate to be correlated with a test of information processing speed and verbal learning/memory (Benedict et al., 2009). Yet in the work of both Benedict and colleagues (2009) and Pravatà and colleagues (2017) thalamus volume performed similarly to caudate volume. In the current study, thalamus volume was associated only with Simple RT Task – ISD. Other work examining ISD in MS has focused on

functional MRI instead of structural MRI measures, and is discussed in the Implications, Limitations, and Future Research section, below (*Chapter 6.4.5*).

6.4.3 Standard Neuropsychological Tests and Structural MRI Measures

Of the three standard neuropsychological test scores that comprise the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), two had no association with structural MRI measures: the Symbol Digit Modalities Test (SDMT) Total Score, commonly associated with information processing speed, and the California Verbal Learning Test – Second Edition (CVLT-II) Total Immediate Recall, commonly associated with verbal learning and memory. The Brief Visuospatial Memory Test – Revised (BVMT-R) Total Immediate Recall, commonly associated with visual learning and memory, was correlated with BPF, white matter lesion volume, and grey matter lesion volume. These limited associations were found despite baseline RT not being statistically accounted for in the standard neuropsychological test scores, as was done for the DalCAB measures. These results fit into previous work demonstrating mixed or limited associations between standardized cognitive testing and structural MRI measures in MS. For example, in their meta-analyses Rao and colleagues (2014) reported that only two of seven studies found significant correlations between the SDMT and brain atrophy.

Although the BVMT-R Total Immediate Recall was associated with some structural MRI measures, described above, this standard neuropsychological test score was the only score (of the 11 examined) that did not differ between MS and

control participants in *Chapter 3.2.10* (*Standard Neuropsychological Tests – Performance Between Groups*). Therefore, although this test appears to be associated with MS pathology, it may not be a strong test for identifying cognitive impairment in MS.

Many standard neuropsychological tests are commonly described as representing one cognitive domain, despite the tasks requiring an array of cognitive abilities. This lack of precision in assessing cognitive functions becomes particularly problematic when attempting to associate a specific cognitive deficit with CNS changes on MRI. Although some MRI measures have shown promise, such as those selected to be used in the current analyses, these problems will likely continue to persist as long as the same standard neuropsychological tests continue to be used exclusively. Based on the current study, the addition of a measure of response speed would be beneficial.

6.4.4 Clinical Characteristics and Structural MRI Measures

For completeness of this chapter, associations between demographics (age, years of education), health-related quality of life [HRQoL; single attribute utility score on the Health Utility Index (HUI)], clinical characteristics (EDSS, years since onset) and the structural MRI measures were examined. There were no significant associations between EDSS, HRQoL on the HUI, and years of education. Previous analyses in this thesis have shown EDSS and HRQoL to be highly correlated (r_s = -.429, see *Chapter 3.2.7 DalCAB Correlations with Clinical Characteristics – Ecological Validity*) and it could therefore be expected that these variables might perform similarly. The lack of association between structural MRI characteristics,

such as lesion volumes, and EDSS or HRQoL on the HUI, is consistent with the "clinical-radiological paradox", the term used to describe the weak association between the severity of clinical disability and volume of white matter lesions imaged using MRI (Barkhof, 2002). Barkhof (2002) has previously highlighted the limitations of EDSS and limitations of structural imaging, in that structural imaging fails to capture functional loss or plasticity, as two factors that contribute to this paradox.

Years since onset of MS had the most associations with structural MRI measures, all in intuitive directions; As years since MS onset increases so does white and grey matter lesion volumes (positive correlations), and as years since MS onset increases deep grey matter structure volumes and brain parenchymal tissue volumes decrease (negative correlations). Although this sample of persons with MS were selected to have relatively low neurologic disability based on EDSS, the number of years since MS onset present in the sample was quite varied (range: 0 to 37 years, interquartile range 7 to 18 years), highlighting that structural brain changes that occur over time are not always reflected by EDSS scores.

In summary, attention network performance as measured by the DalCAB was not associated with structural MRI measures (aim 1), beyond baseline RT. Simple RT Task – ISD had numerous associations with structural MRI measures and caudate volume was associated with ISD on various tasks, however, the remaining ISD measures had limited or no association with structural MRI (aim 2).

6.4.5 Implications, Limitations, and Future Research

The current analyses explored the association between attention network performance and ISD in MS and structural brain measures on MRI, finding that there were relatively few associations between the two in the current sample. Although correlational analyses can be useful for broad exploratory analyses, the current sample size (in particular the smaller control group size; n_{MS} = 39, $n_{control}$ = 21) and highly correlated independent variables of interest (i.e., the structural MRI measures) created substantial limitations in conducting further multi-variable regression models. These non-significant results and statistical limitations make it difficult to draw inferences on how the neuroanatomical correlates of Posner and Petersen's (1990) attention network model may look in this MS population. Although it remains true that cognitive assessment measures that more accurately identify the specific cognitive function being assessed and relate to neuroanatomical areas would be an important tool in understanding the variability in cognitive functioning in MS and developing effective therapies, the current analyses suggest a different approach is needed in examining the DalCAB and MRI measures.

Structural MRI measures have continued to account for only some of the variation in cognition in MS and a shift toward functional imaging has begun. Schoonheim and colleagues (2015) have proposed the theory of decreasing network efficiency as structural damage due to MS accumulates, which aligns with previous work demonstrating that decreased fiber tract integrity between relevant areas is associated with domain-specific impairments (i.e., disconnectionist model;

Dineen et al., 2009). Other proponents of a disconnectionist model posit that given some tracts have greater importance to the various cognitive networks, it is the location of lesions and microscopic tissue abnormalities instead of the volume of lesions that has the greatest impact (Rocca et al., 2015). Authors have begun to demonstrate associations between lower cognitive function in MS, decreased white matter integrity (Akbar et al., 2010; Hulst et al., 2013; Yu et al., 2012), and decreased connectivity in grey matter networks (Rimkus et al., 2019). Wojtowicz and colleagues (2014) were the first to examine functional MRI and ISD of attention network performance in an MS population. Their work is consistent with the theory of "network collapse", as increased ISD (i.e., less stability in performance) was associated with decreased connectivity between frontal regions involved in meta-cognitive functions, suggested by the authors to represent decreased integrity between those neural regions. The current analyses demonstrated that even small changes in ISD on a simple RT task can be associated with changes in neurophysiology. Future work on correlates of behavioural measures reflecting attentional networks should examine functional measures of network efficiency, which may better explain variability in cognitive functioning compared to structural measures.

Given that performance on all three attention networks differed between MS and control participants in the current study (see *Chapter 3.2.4 Differences in Attention Network Performance Between Groups – Known Groups Validity*), it could be expected that reduced network efficiency would be observed across all three networks. Based on Petersen and Posner (2012), this would include the

parietal cortex with connections to frontal areas such as the frontal eye fields and ventral frontal cortex (orienting network), systems within the right cerebral cortex (vigilance network), and systems within the lateral frontal and parietal regions (the frontoparietal component; executive control network). Although Petersen and Posner (2012) also describe a cinguloopercular component of the executive control network (operating within the medial frontal/cingulate cortex and anterior insula), the frontoparietal component appeared to be more affected in this sample of persons with MS compared to the cinguloopercular component (See *Chapter 3.3 Discussion*), which may be reflected in future functional imaging work.

Chapter 7. Conclusion

The current thesis has investigated attention network performance in a large sample of persons with relapsing-remitting multiple sclerosis (RRMS) with relatively low neurologic disability based on the Expanded Disability Status Scale (EDSS). Comprehensive data collection, including standard neuropsychological tests, questionnaires regarding common symptoms in MS, the Dalhousie Computerized Attention Battery (DalCAB), and magnetic resonance imaging scans (MRI; for a sub-set) allowed for a thorough evaluation of attentional abilities and related factors in this population. The DalCAB is a novel computerized measure of attention network performance and was used here for the first time in a MS population. This measure captures the multiple factors that comprise attention, providing a more detailed appraisal of this cognitive domain compared to paper-and-pencil tasks.

7.1 Assessing Networks of Attention in Multiple Sclerosis and Validating the Dalhousie Computerized Attention Battery (Thesis Aim 1)

Persons with MS differed from age-, gender-, and education-matched healthy controls in their performance on all three attention networks: orienting, vigilance, and executive control. Yet within each of those networks, performance on some attention measures did not differ from controls. This thesis is the first to provide an assessment of attention at this level of detail in this population, and suggests that employing tests that generate only a single score to represent attention network performance may not provide the diversity of information

necessary to understand how attention networks are affected in individuals with MS.

Initial validation of the DalCAB in an MS population was conducted, comparing performance on the DalCAB between known groups, to relevant patient outcomes and characteristics, and to standard neuropsychological tests. MS clinics are searching for methods of reducing the time and resource demands required of neuropsychological assessments. The current thesis has provided the foundation of data necessary to adopt the DalCAB on a trial basis in a clinical setting, however, further validation of the DalCAB in clinical settings is required.

Many associations between the standard neuropsychological tests and DalCAB attention network measures were observed, providing support for the multi-factorial nature of commonly used paper-and-pencil standard neuropsychological tests. These associations suggest that an individual's various attention abilities would affect their performance on these standard neuropsychological tests. Specifically, the Symbol Digit Modalities Test (SDMT), the most commonly recommended test for cognitive functioning in MS in North America and Europe, was associated with performance across all three attention networks even after accounting for baseline reaction time (RT) differences between groups. This provides support for the assumption made by many research groups: the SDMT assesses aspects of attention in addition to information processing speed.

7.2 Attention Network Performance and Intra-Individual Variability in Persons with MS Not Impaired on Standard Neuropsychological Tests (Thesis Aim 2)

Standard neuropsychological tests included in the BICAMS classified 37.5% of the MS sample as impaired on at least one task. This is consistent with previous work indicating that individuals who are classified as “low neurologic disability” using EDSS still experience cognitive impairments.

The current thesis demonstrated that slowed RT and decreased attention network performance on the vigilance and executive control networks can be detected in persons with MS who do not exhibit cognitive deficits as operationalized by commonly used neuropsychological tests [i.e., the Brief International Cognitive Assessment for MS (BICAMS)]. Assessment tools that allow for the detection of subtle cognitive changes, especially after having accounted for differences in baseline RT, may allow for further understanding in the variability of MS prognoses and treatment outcomes. Based on the current thesis, the RT-based DalCAB tasks show promise for being used clinically to detect and monitor early cognitive changes in MS.

Intra-individual variability (IIV), a behavioural measure of central nervous system (CNS) integrity, has shown promise in previous work as a sensitive measure of cognitive change in MS. The current thesis found individual standard deviation (ISD) to be a more valuable measure of IIV in an MS population compared to coefficient of variation (CoV), consistent with previous work in MS. Although both ISD and CoV account for baseline RT differences between groups,

ISD also accounts for variability due to practice effects over the course of many trials.

The current thesis built on previous work in ISD, demonstrating that ISD may be used to detect changes in CNS integrity in persons with MS who do not exhibit cognitive deficits on commonly used neuropsychological tests (i.e., the BICAMS). This measure can be calculated from any computerized task that measures response speed over numerous trials, making it an additional metric that can be calculated in existing testing protocols.

7.3 The Effect of Fatigue, Pain, Anxiety, and Depression on Attention Network Performance in Multiple Sclerosis (Thesis Aim 3)

Self-reported symptoms of depression, anxiety, fatigue, and pain did not account for variability in attention network performance on the DalCAB after variation due to baseline RT was accounted for. As the DalCAB is a measure of cognitive functioning that appears to be unaffected by these common symptoms, this is yet another promising feature with regard to its utility in a MS clinic setting.

ISD on some tasks does appear to be affected by common symptoms in MS such as depression, fatigue, and pain, however, the results in the current sample are conflicting with the limited existing research in this area. This limited work has been conducted with regard to depression and anxiety only, and the relationships between ISD, fatigue, and pain have not been examined previously in MS. ISD was affected by these symptoms in the current sample, indicating that this may be a useful measure for capturing objective cognitive changes in

individuals who report an adverse impact of their symptoms of fatigue and pain on their cognitive functioning.

7.4 Examining Associations Between Structural Brain Changes on Attention Network Performance in Multiple Sclerosis (Thesis Aim 4)

The current thesis builds on and contributes to work on structural MRI correlates to cognitive functioning in MS. Although the majority of structural MRI measures differed between the MS and control groups, brain parenchymal fraction (BPF) did not, possibly reflecting that this study sample was comprised of persons with RRMS with low neurologic disability as measured by EDSS, and used a small MRI slice size (i.e., 1mm).

Cognitive assessments that more accurately isolate specific cognitive functions and are reliably associated with specific neuropathological features of MS would be an important tool in understanding the variability in cognitive functioning in MS. Understanding this variability is necessary in facilitating the development of effective therapies. The limited exploratory correlations used in the current thesis clearly suggest that the DalCAB measures of attentional network functioning do not reflect broad, whole brain measures of structural change such as total lesion volumes or BPF, nor are they easily attributable to regional subcortical volumetric changes. Future work looking to understand changes in neuroanatomy that lead to attention network deficits in MS should examine structural and functional connectivity using more advanced multimodal MRI such as diffusion tensor imaging and functional-MRI.

ISD on the Simple RT Task, although had the smallest effect size when examining between group differences, was the only ISD measure to be correlated with the majority on the structural MRI measures. MRI analyses in the current thesis demonstrate that even small changes in ISD on a simple RT task relate to changes in neuroanatomy, consistent with ISD being a sensitive behavioural indicator of CNS integrity.

7.5 Directions for Future Work

Although the thesis has provided initial validation for the DalCAB in a MS population, further validation is required in less restricted MS samples (e.g., different MS sub-types, EDSS ranges, other cultural groups) if the testing battery is to be used in MS clinics more broadly. If the DalCAB were to be implemented as a cognitive testing tool in an MS clinic, data regarding the clinical value of assessing attention network performance would be necessary: Does attention network performance longitudinally predict aspects of prognosis such as progression of physical disability or cognitive impairments, social outcomes such as loss of employment, or response to disease modifying drugs? Does attention network performance correspond to performance on real-world tasks such as instrumental activities of daily living (e.g., cooking, cleaning) or a person's ability to live independently?

This thesis has highlighted the lack of precision when assessing cognitive functions with standard neuropsychological tests. This lack of precision becomes particularly problematic when attempting to associate a specific cognitive deficit with CNS changes on MRI. Attention network performance on the DalCAB has

similarly shown few associations with structural MRI measures, however, changes in structural and functional connectivity as they relate to attention network performance in MS have not yet been examined.

The knowledge generated from the thesis has contributed to understanding attention network performance in MS and has created new questions on the topic to be answered in future work.

Appendix A. Supplementary Tables

Supplementary Table 1. Record of Missing Data.

Group	*N*	Missing Data	Reason
MS	2	First language	Had not started collecting this variable.
	1	Snellen Eye Chart – left eye	Missing score for left eye, however, right eye is sufficient to meet inclusion criteria.
	4	DalCAB Dual Task	Participants did not complete task correctly.
Control	1	DalCAB Visual Search Task	Examiner error. Task not administered.
	1	DalCAB Vertical Flanker Task	Examiner error. Wrong version of task administered.
	1	DalCAB Simple RT Task; Variable: "Response stimulus interval effect"	Participant did not have enough correct trials to calculate the effect.
	1	SDMT Total	Examiner error. Task was administered incorrectly.

Note. Two MS participants in the MS-MRI group completed 2 additional DalCAB tasks due to administrator errors. These were not administered to the rest of the participants and this data was not included in the current study, however, could have led to increased fatigue in those two participants.

Supplementary Table 2. Description of DalCAB Variables.

Network of Attention	DalCAB Variable	Description
Baseline RT	SRT – Mean RT	Time it takes for participant to click the mouse button when target appears. Measures response readiness and sensorimotor RT, however, is being used to represent only sensorimotor RT in the current thesis.
Vigilance	VS – Feature Search Mean RT	Mean RT of responses for feature search trials (i.e., trials where the target stimulus is a different color than distractors and easy to spot). Can be considered to be a visual CRT task.

Network of Attention	DalCAB Variable	Description
Vigilance	VS – Feature Search Set Size Effect (RT)	Difference in RT when provided the largest feature search set size compared to the smallest set size.
	CRT-SRT – Decision Speed (RT)	Time it takes for participant to decide which mouse button to click. Calculated using SRT and CRT Tasks.
	SRT – Response Stimulus Interval Effect (RT)	Response time for the longest response stimulus interval minus the response time of the shortest response stimulus interval. Individuals are expected to be faster for longer response stimulus intervals (i.e., temporal preparation effect).
	GNG – 20% Vigilance Decrement (RT)	Change in RT between last 1/3 and first 1/3 of responses during 20%-go frequency condition. Measure of change in sustained attention, as sustained attention is necessary when frequency of "go" responses is low. Decrement in vigilance overtime, that could represent fatigue.
	DT – Switch-Cost (RT)	Difference in RT of response selection between non-switch trials (no change in response from the previous trial) and switch trials (a change from the response of the previous trial).
	CRT – Standard Deviation	Amount an individual varies in their own response times on the CRT Task.
	SRT – Standard Deviation	Amount an individual varies in their own response times on the SRT Task.
Orienting	GNG – Proportion Effect (RT)	Difference in RT between the high-frequency go condition (80% go) and low-frequency go condition (20% go).
	VS – Conjunction Search Mean RT	Mean RT of responses for conjunction search trials (i.e., trials where the target stimulus shares some features of the distractors and is more difficult to spot).

Network of Attention	DalCAB Variable	Description
Orienting	VS – Conjunction Search Set Size Effect (RT)	Difference in RT when provided the largest conjunction search set size compared to the smallest set size.
	GNG – 20% Go Percent False Alarm	Percent of commission errors during trials in the 20%-go frequency condition. Measure of ability to inhibit responses.
Executive Control	GNG – 80% Go Percent False Alarm	Percent of commission errors during trials in the 80%-go frequency condition. Measure of ability to inhibit responses, particularly relevant when frequency of "go" responses is high.
	GNG – 80% Vigilance Decrement (RT)	Change in RT between last 1/3 and first 1/3 of responses during 80%-go frequency condition. Measure of change. Represents a decrement in vigilance overtime, that could represent fatigue.
	IM – Mean RT	Mean RT for trials where a medium sized memory set was given.
	IM – Set Size Effect (RT)	Difference in RT when provided the largest memory set size compared to the smallest. Individuals are expected to be slower for larger set sizes (i.e., set size effect). Represents time spent scanning memory.
	IM – Set Size Effect (Accuracy)	Difference in accuracy when provided the largest memory set size compared to the smallest. Reflects working memory capacity.
	IM – Target Absent Effect (RT)	Difference in RT between trials where the target was present in the memory set (i.e., participants have to go through memory set only until they reach the target) and trials where the target was not present in the memory set (i.e., participants have to filter through entire memory set to determine target is absent). May represent proactive interference.
	VF – Congruency Effect (Accuracy)	Difference in accuracy of response selection between non-congruent trials (flankers not consistent with target stimuli) and congruent trials (flankers consistent with target stimuli).

Network of Attention	DalCAB Variable	Description
Executive Control	CRT – Switch-Cost (Accuracy)	Difference in accuracy of response selection between non-switch trials (no change in response from the previous trial) and switch trials (a change from the response of the previous trial).
	DT – Cost (RT)	The decrease in RT due to interference of the second task or increase in attentional load (i.e., working memory load effect). Computed by comparing CTR Task to Dual Task.

Note. Shading indicates which variables differed between the MS and control groups, see *Chapter 3.2.4 (Differences in Attention Network Performance Between Groups)*; RTs are in milliseconds; Variable names listed here are consistent with Jones and colleagues (2015): SRT = Simple Reaction Time, CRT = Choice Reaction Time, DT = Dual Task, GNG = Go-No-Go, IM = Item Memory (also referred to as the Sternberg Task), VF = Vertical Flanker, VS = Visual Search. See Jones and colleagues (2015) for further description of how variables were calculated.

Supplementary Table 3. Labels Used for Reporting Strength of Correlations and Effect Sizes.

Statistic	Magnitude and Label		Reference
Effect Size – Partial Eta Squared (η^2_p)	.01 .09 .25	Small Medium Large	Cohen (1992)
Correlations	.1 – .3 .4 – .6 .7 – .9 1.0	Weak Moderate Strong Perfect	Dancey (2009)

Supplementary Table 4. Variance in Attention Network Performance Accounted for by Self-Reported Symptoms.

Associated Network of Attention	DalCAB Variables	Fatigue	Pain	Anxiety	Depression
Vigilance	VS Feature Search – Mean RT	$F(1,102) = .321$, $p = .572$	$F(1,102) = 3.196$, $p = .077$	$F(1,102) = .171$, $p = .680$	$F(1,102) = .089$, $p = .766$
	DT – Switch-Cost (RT)	$F(1,98) = .005$, $p = .946$	$F(1,98) = .315$, $p = .576$	$F(1,98) = 2.301$, $p = .133$	$F(1,98) = .050$, $p = .823$

Associated Network of Attention	DalCAB Variables	Fatigue	Pain	Anxiety	Depression
Vigilance	CRT – Standard Deviation	$F(1,102) = 2.303$, $p = .132$	$F(1,102) = 2.835$, $p = .095$	$F(1,102) = .444$, $p = .507$	$F(1,102) = .095$, $p = .758$
Orienting	VS Conjunction Search – Mean RT	$F(1,102) = .489$, $p = 0.486$	$F(1,102) = 2.943$, $p = .089$	$F(1,102) = .001$, $p = .973$	$F(1,102) = .072$, $p = .789$
	VS Conjunction Search – Set Size Effect (RT)	$F(1,102) = .634$, $p = .428$	$F(1,102) = 3.437$, $p = .067$	$F(1,102) = .044$, $p = .834$	$F(1,102) = .032$, $p = .858$
Executive Control	GNG – 20% Go Percent False Alarm	$F(1,102) = .087$, $p = .769$	$F(1,102) = 1.991$, $p = .161$	$F(1,102) = .154$, $p = .695$	$F(1,102) = .072$, $p = .789$
	IM – Mean RT	$F(1,102) = 1.525$, $p = .220$	$F(1,102) = 2.139$, $p = .147$	$F(1,102) = 2.577$, $p = .111$	$F(1,102) = 1.101$, $p = .296$
	IM – Target Absent Effect (RT)	$F(1,102) = .635$, $p = .427$	$F(1,102) = .682$, $p = .411$	$F(1,102) = .974$, $p = .326$	$F(1,102) = .629$, $p = .429$
	DT – Cost (RT)	$F(1,98) = .671$, $p = .415$	$F(1,98) = 1.745$, $p = .190$	$F(1,98) = 2.571$, $p = .112$	$F(1,98) = 1.153$, $p = .285$

Appendix B. Detailed MRI Procedure as Designed by Carl Helmick

MRI Conversion and Defacing.

DICOM sequences were converted into compressed 3D NIFTI image files using the image conversion tool "dcm2niix" (Li et al., 2016). All anatomical scans were defaced (structurally anonymized) to zero-fill face, neck, and ear voxels. This was conducted with a linear 12-Degrees-of-Freedom registration of MNI152 Template[2] to the participant image using FLIRT (Jenkinson et al., 2002; Jenkinson & Smith, 2001), followed by inverting the resulting affine matrix, applying the inverse transform to FSL's facemask (MNI152_T1_1mm_BigFoV_facemask.nii), and finally, multiplying the facemask to the participant's image to zero-fill voxels corresponding to face, neck, and ears. The defaced images were visually reviewed to ensure identifying features were properly removed, and that subject brain images were free of artifacts and anomalies.

MRI Preprocessing.

Each participant's three structurally-anonymized images (i.e., T1, T2, and T2 FLAIR) were preprocessed to include (1) cropping, (2) bias (i.e., inhomogeneity) correction, (3) ACPC-alignment[3] to MNI152 Template space.

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[2] The Montreal Neurologic Institute (MNI) 152 template is a brain template created from spatially-aligning and averaging the whole-brain scans of 152 healthy adults (Mazziotta et al., 2001).

[3] ACPC-alignment (where anterior commissure and posterior commissure are horizontally aligned on same slice) is useful for structural analysis to provide a consistent orientation for visual review and locating neuroanatomical landmarks and substructure boundaries.

Cropping was done to remove excess neck and empty slices outside the head. For this, 12-Degrees-of-Freedom linear (FLIRT) and nonlinear warp (FNIRT, with 10mm-spacing) registration of the MNI152 Template (MNI152_T1_2mm) was calculated to the participant T1-weighted image. The warp was applied to align the MNI152 whole-head image with the participant image (APPLYWARP): (1) thresholding this image at 100 to create an head-mask (FSLMATHS), (2) then determining the minimum bounding-box coordinates X,Y,Z of the head-mask (FSLSTATS), and (3) using these coordinates to crop the participant T1-weighted image (FSLROI). Each step in this preprocessing used an atlas registration-based approach including both linear and nonlinear registrations.

To do bias correction, the cropped T1-weighted image was registered to the MNI152 Template (MNI152_T1_2mm) image both linearly and nonlinearly; the resulting warp was inverted and applied to transform the MNI152 brain mask (MNI152_T1_1mm_brain_mask.nii) into participant-space. This mask was used to create an initial T1-weighted skull-stripped “brain”. A bias estimate image was calculated from this initial brain image using FAST (Zhang et al., 2001) and divided into the cropped whole-head participant T1-weighted to produce a bias-corrected whole-head T1-weighted image.

ACPC-alignment was calculated in two stages. First, a more accurate skull-stripped brain image was created by linearly and nonlinearly registering the cropped and bias-corrected whole-head T1-weighted to the MNI152 Template (MNI152_T1_1mm) and inverting the resulting warp and applying to the MNI brain mask (MNI152_T1_1mm_brain_mask.nii). Then, masking the bias-corrected

image to produce a T1w brain image. Second, this T1-weighted brain image was linearly registered with 12-Degrees-of-Freedom to the MNI152 Template (MNI152_T1_1mm_brain.nii). The resulting affine matrix was reduced from 12-Degrees-of-Freedom to a 6-Degrees-of-Freedom “rigid-body” matrix. This rigid-body transformation matrix was then applied to the cropped and bias-corrected whole-head T1-weighted image to effectively center it into MNI152 Template space while maintaining participant size and shape.

After completing these preprocessing steps on the T1-weighted image, the T2-weighted and T2-weighted FLAIR images were bias-corrected similar to the T1-weighted, and co-registered to the ACPC-aligned T1-weighted image with a rigid-body linear registration (using the FSL "FLIRT" program; Jenkinson et al., 2002; Jenkinson & Smith, 2001).

MRI Analyses.

Analyses steps include (1) lesion segmentation, (2) lesion-filling, (3) final tissue segmentation, (4) final linear and non-linear MNI152 Template registrations, (5) subcortical structure segmentation and (6) volumetric value reporting.

Automated lesion segmentation was conducted using the Lesion Segmentation Toolbox (LST) to estimate the volume of lesioned tissue for each participant. The ACPC-aligned bias-corrected T1-weighted and T2-weighted FLAIR were input to LST, and a lesion mask was generated using the Lesion Growth Algorithm (Schmidt et al., 2012) with an initial threshold of 0.3. FSL lesion-filling tool (lesion_filling) was used to replace lesion-labelled voxels on the ACPC-aligned T1-weighted image with normal-appearing white-matter voxel intensity

values. MS lesions often appear as hypointense “black-holes” on a T1-weighted image and without lesion-filling, these will often be misclassified during tissue segmentation as gray-matter or cerebrospinal fluid instead of white matter.

Tissue segmentation was completed on the lesion-filled T1-weighted brain using the FSL “FAST” program (Zhang et al., 2001) to create final tissue masks for white matter, grey matter, and cerebral spinal fluid. As a quality check on the lesion segmentation, lesion-overlap masks were created between the lesion mask and each white matter, grey matter, and cerebral spinal fluid mask. Both tissue and overlap volumes were reported, and proportion of lesion overlap with each tissue was investigated to ensure lesion voxels predominantly overlapped white matter >80%.

Linear and non-linear registration tools typically work by locating matching control-points in both input and reference images and then calculating the geometrical transformation to align input to reference. However, the presence of abnormal tissue in a typical MS brain generates control that cannot be matched in the MNI152 Template brain, causing registration failures or incorrect registration results. Here, final linear 12-Degrees-of-Freedom and non-linear registrations to the MNI152 Template (MNI152_T1_1mm) were calculated using the cropped, bias-corrected, ACPC-aligned T1-weighted brain image. The inverted lesion-mask as weighted-option was selected for both the FSL “FLIRT” and “FNIRT” programs to restrict control-point matching outside of lesions in normal brain tissue to provide accurate registrations to MNI152 Template. A MNI152 brain scalar value was derived the summation of scaling values from the final linear transformation matrix.

This scalar value represents the degree of physical scaling required to spatially normalize each participant brain to the MNI152 Template.

Subcortical structure segmentation was performed using the FSL “FIRST” program (Patenaude et al., 2011) on the lesion-filled T1-weighted image with the participant to MNI152 linear transform matrix to create structure masks delineating the thalamus, hippocampus, caudate, and putamen.

The following anatomical volumetric measures were derived: estimated total brain volume, estimated white matter volume, estimated grey matter volume, cerebral spinal fluid volume, estimated thalamus volume, estimated hippocampus volume, estimated putamen volume, estimated caudate volume, lesion volume, volume of lesion overlap with each tissue type and structure (e.g., lesion overlap in white matter), and the MNI152 brain scalar value. As estimated volume values were calculated using participant’s lesion-filled T1-weighted image, lesion overlap values were then subtracted from their corresponding estimated volume value to give the true volume estimate. Volume values are in mm^3.

Prior to conducting group analyses involving volume, volume values were multiplied by each participant’s MNI152 brain scalar value in order to scale volumes into MNI152-space. This scaling process allowed for direct volume comparisons between individuals by adjusting for individual brain size.

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