Detecting Cognitive Dysfunction in Multiple Sclerosis: Assessing the Validity of a Computer Generated Battery

by

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Institute of Medical Science
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Abstract

Approximately half of Multiple Sclerosis (MS) patients experience cognitive deficits. Accessing neuropsychological assessment can be challenging due to the considerable time, expense, and expertise required for test administration. Computerized cognitive testing has been proposed as an alternative. The objective was to validate a computer generated cognitive screen for MS patients. Ninety-nine MS patients and 98 healthy controls completed the computerized battery consisting of the Stroop, Symbol Digit Modalities Test (C-SDMT), Paced Auditory Serial Addition Test (PVSAT-2, PVSAT-4), and simple and choice reaction time tests. The Minimal Assessment of Cognitive Function in MS (MACFIMS) was used to define cognitive impairment in the MS sample. A combination of the C-SDMT, PVSAT-2, PVSAT-4 had a sensitivity of 83.3% and specificity of 87.7% in detecting cognitive impairment. Each measure had good test-retest reliability (p < 0.001). High sensitivity and specificity, and brevity emphasize the usefulness of the computerized cognitive screen in busy MS clinics.
Contributions

Helen Lapshin was responsible for completing the literature search, planning the study design with the help of Dr. Feinstein, recruitment of all the MS patients and half (46) of the healthy subjects, completing the neuropsychological testing of all the MS patients (both the computerized and conventional batteries) and half (46) of the control subjects (computerized testing only), analyzing and interpreting the data, and writing and editing the thesis.

Dr. Anthony Feinstein, as the supervisor, was responsible for conceptualizing the study, planning the study design, assisting with data analysis and interpretation, editing the thesis, and general supervision of the study.

Dr. Paul O'Connor, as program advisory committee member, assisted in planning the study design, as well as assisted with recruitment, data interpretation, and editing of the thesis.

Dr. Krista Lanctôt, as program advisory committee member, assisted in planning the study design, assisted with recruitment, data interpretation, and editing of the thesis.

Dr. Alex Kiss assisted with statistical analysis.

Nancy Blair, Nancy Kou, Arielle Marks, and Elizabeth Waknine, from Dr. Feinstein’s lab, assisted with recruiting and testing half (52) of the healthy participants.

Dr. Liesly Lee, Kathleen Carr, and Melanie Winters from the Sunnybrook Multiple Sclerosis clinic, and Sheryl Clarke from St. Michael's Multiple Sclerosis Clinic assisted with the recruitment of MS patients.
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List of Abbreviations

7/24 – 7/24 Spatial Recall Test
10/36 – 10/36 Spatial Recall Test
ANAM – Automated Neuropsychology Assessment Matrix
ANART – American National Adult Reading Test
ANT – Amsterdam Neuropsychological Tasks
AUC – area under the curve
BDI – Beck Depression Inventory
BICAMS – Brief International Cognitive Assessment for Multiple Sclerosis
BRB-N – Brief Repeatable Battery of Neuropsychological Tests
BVMT-DR – Brief Visuospatial Memory Test - Revised - Delayed Recall
BVMT-R – Brief Visuospatial Memory Test - Revised
BVMT-TOT – Brief Visuospatial Memory Test - Revised - Total Recall
C-SDMT – Computerized Symbol Digit Modalities Test
CDR – Cognitive Drug Research battery
CIS – clinically isolated syndrome
COWAT – Controlled Oral Word Association Test
CNS – central nervous system
CRT – Choice Reaction Time
CRT-SRT – Choice Reaction Time minus Simple Reaction Time
CSF – cerebrospinal fluid
CSI – Cognitive Stability Index
CTIP – Computerized Tests of Information Processing
CVLT-II – California Verbal Learning Test - II
CVLT-DR – California Verbal Learning Test - II - Delayed Recall
CVLT-TOT – California Verbal Learning Test - II - Total Recall
DGM – deep grey matter
D-KEFS – Delis-Kaplan Executive Function System
D-KEFS-DS – Delis-Kaplan Executive Function System - Description Score
D-KEFS-SS – Delis-Kaplan Executive Function System - Sorting Score
DSS – Disability Status Scale
DSST – Digit Symbol Substitution Test
DTI – diffusion tensor imaging
EDSS – Expanded Disability Status Scale
fMRI – functional magnetic resonance imaging
HAD – Hospital Anxiety and Depression Scale
ICC – intraclass correlation coefficient
JLO – Judgment of Line Orientation
MACFIMS – Minimal Assessment of Cognitive Function in Multiple Sclerosis
MADRS – Montgomery and Asberg Depression Rating Scale
MCCB – Mindstreams Computerized Cognitive Battery
MMSE – Mini-Mental State Examination
MRI – magnetic resonance imaging
MS – multiple sclerosis
MSFC – Multiple Sclerosis Functional Composite
MSNQ – Multiple Sclerosis Neuropsychological Questionnaire
MTI – magnetization transfer imaging
MTL – mesial temporal lobe
MTR – magnetization transfer ratio
MWCST – Modified Wisconsin Card Sorting Test
NABT – normal-appearing brain tissue
NAGM – normal-appearing grey matter
NAWM – normal-appearing white matter

NPV – negative predictive value

NPSBMS – Neuropsychological Screening Battery for Multiple Sclerosis

PASAT – Paced Auditory Serial Addition Test

PASAT-3 – Paced Auditory Serial Addition Test (3 second trial)

PASAT-2 – Paced Auditory Serial Addition Test (2 second trial)

PCC – posterior cingulate cortex

PFC – prefrontal cortex

PPMS – primary progressive multiple sclerosis

PPV – positive predictive value

PRMS – progressive relapsing multiple sclerosis

PVSAT – Paced Visual Serial Addition Test

PVSAT-4 – Paced Visual Serial Addition Test (4 second trial)

PVSAT-2 – Paced Visual Serial Addition Test (2 second trial)

ROC – receiver operating characteristic

RBMT – Rivermead Behavioural Memory Test

RRMS – relapsing-remitting multiple sclerosis

SDMT – Symbol Digit Modalities Test

SPMS – secondary progressive multiple sclerosis

SRT – Selective Reminding Test

SRT – Simple Reaction Time

STROOP – Stroop Colour-Word Test

TAP – Computerized Attention Test Battery

VEP – visual evoked potential

WAIS-R – Wechsler Adult Intelligence Scale – Revised

WCST – Wisconsin Card Sorting Task
WLG – Word List Generation Task
Chapter 1
Introduction

1.1 Background

1.1.1 Overview and History

There are numerous historical accounts of case studies suggestive of the effects and symptoms of multiple sclerosis (MS) although it was not until the publications of the illustrations of Robert Carswell (1793-1857) in *Pathological Anatomy; Illustrations of Elementary Forms of Disease* (Carswell, 1838) and Jean Cruveilhier (1791-1874) in *Anatomie pathologique du corps humain; descriptions avec figures lithographiées et coloriées; des diverses alterations morbides dont le corps humain est susceptible* (Cruveilhier, 1829-1842) that the first clinical and pathological descriptions of the disease were made. The drawings depicted the brainstems and spinal cords of several patients who had, in life, suffered from symptoms suggestive of those associated with modern day multiple sclerosis. These illustrations showed visible patches or plaques, which Cruveilhier called *grise masses disseminées*. It was Jean-Martin Charcot, however, who was the first to distinguish multiple sclerosis as a separate disorder, combining previous accounts, including those of Carswell and Cruveilhier, into a global description of the disease (Charcot, 1868). Charcot's recognition of *sclérose en plaques* as a separate disease saw an increase in the disorder's frequency from a rare phenomenon in the 1870s to the most common cause of neurological disability affecting young and middle aged adults today (Compston et al., 2005).

MS is a demyelinating autoimmune disease that affects both white and grey matter of the central nervous system (CNS) and is believed to be influenced by both genetic and environmental factors (Noseworthy et al., 2000). The overall prevalence in Canada is 240 for every 100,000 people (Beck et al., 2005), which translates into 75,000-80,000 people with MS in Canada.

1.1.2 Pathogenesis

Although the cause of MS is unknown, the most popular theory regarding the biological mechanisms behind the disease is that it is an autoimmune disorder of the central nervous system in which myelin (or a component thereof) is the principal target of activated elements of the immune system including autoreactive T and B cells, macrophages and complement. Within the CNS these inflammatory cells damage myelin, myelin-generating oligodendrocytes, and axons.
Demyelination and axonal damage result in impaired axonal conduction which in turn gives rise to neurologic symptoms. The areas of demyelination seen in the brain, spinal cord, and optic nerves are pathologically called ‘plaques’. The unprotected axons are vulnerable to the effects of antibodies and cytokines in this inflammatory milieu and are prone to damage. The inflammatory response may resolve on its own and some degree of remyelination takes place with the help of oligodendrocyte precursor cells, especially in the relapsing-remitting form of the disease. This regeneration of myelin and return of axonal conduction is thought to be one of several mechanisms that mediate clinical remission (Kutzelnigg et al., 2005; Noseworthy et al., 2000).

New and active focal white matter lesions, or plaques, are characteristic of relapsing-remitting MS (RRMS) whereas secondary progressive MS (SPMS) and primary progressive MS (PPMS) are characterized by both plaques and more diffuse axonal injury of the normal-appearing white matter (Kutzelnigg et al., 2005). Cortical demyelination and axonal damage are, however, present from the beginning of the disease and in an individual case it is not possible to look at the brain pathology and reliably predict the clinical disease phenotype. With increased disease duration and patient age the condition tends to become diffuse with more axonal damage and atrophy.

Recently, brain volume loss, or atrophy, which is related to both white and grey matter, has been highlighted in the pathology of the disease (Grassiot et al., 2009). Magnetization transfer imaging (MTI) and diffusion tensor imaging (DTI) have been helpful in demonstrating early (MTI) and tract-specific (DTI) atrophy. There has also been an increasing interest in grey matter atrophy in recent years, particularly since more powerful magnetic resonance imaging (MRI) have permitted better visualization of the grey matter. Grey matter atrophy may correlate better with clinical measures such as disability and disease duration (Sanfilipo et al., 2005).

1.1.3 Diagnosis and Symptoms

Diagnostic criteria for MS have recently been revised by Polman and colleagues (2005). Usually both clinical and MRI indices are necessary for diagnosis although this is not always the case. For instance, when a patient experiences two or more attacks (i.e., neurological episodes, the causative lesions of which appear to be inflammatory and demyelinating) each lasting at least 24 hours and occurring at least one month apart, and the clinical presentation of the attacks suggests at least two separate lesions, a diagnosis can be made without MRI evidence. On the other hand,
MRI indices are required when the clinical presentation is not as clear cut. Two or more attacks with evidence of only one lesion or one attack with evidence of at least two lesions, for example, must be accompanied by MRI criteria such as two separate T2 lesions disseminated in space (different brain regions) and time (i.e., the second lesion appearing at least 30 days after an initial scan). A diagnosis for progressive MS takes on a different approach. Clinical evidence of disease progression together with MRI lesions in the brain and spinal cord are needed for diagnosis.

When MRI or clinical data are lacking, cerebrospinal fluid (CSF) or visual-evoked potential (VEP) analysis may be used as additional sources of information for a diagnosis of MS, especially if disease is progressive without relapses (McDonald et al., 2001; Polman et al., 2005).

MS is an unpredictable disease and symptoms vary among patients; a poster from the Multiple Sclerosis Society of Great Britain and Northern Ireland "Tear Campaign" (1987-1991) reads "More devastating is the uncertainty" (Compston et al., 2005). At onset patients may experience sensory problems such as numbness and tingling, limb weakness, visual disturbances such as optic neuritis, diplopia (double vision) and vertigo, ataxia, problems with bladder and bowel movements, fatigue, and cognitive dysfunction. Later symptoms include motor difficulties including spasticity and tremors, sensory loss and pain, mood disorders such as depression and emotional lability, dysarthria, dysphagia, and sexual dysfunction (Noseworthy et al., 2000).

1.1.4 Disease Course

MS can take one of several clinical courses, three of which are most common: relapsing-remitting, primary progressive and secondary progressive. The majority (approximately 85%) of patients is afflicted with a relapsing-remitting disease course (RRMS) at onset which is characterized by relapses followed by full or partial recovery and the disease does not progress between relapses (Brassington & Marsh, 1998). RRMS is more common in women, with a ratio of two or three to one (Miller & Leary, 2007). Approximately 50% of RRMS patients go on to develop a secondary progressive course (SPMS) during which the illness progresses with or without relapses, slight remissions, and clinical plateaux (Brassington & Marsh, 1998). Primary progressive MS (PPMS) affects 10-15% of all MS patients (Miller & Leary, 2007). PPMS is characterized by disease progression from onset with infrequent plateaux and rare minor improvement (Brassington & Marsh, 1998). Symptoms of PPMS develop slowly, unlike RRMS, but do not remit (Miller & Leary, 2007). The onset of PPMS occurs, on average, 10 years later
than RRMS (at approximately age 40) (Miller & Leary, 2007). A less common form of MS is progressive relapsing (PRMS), which affects approximately 5% of patients, and is characterized by disease progression from onset with acute relapses. The disease continues to progress between relapses (Lublin & Reingold, 1996).

A benign form of MS, affecting approximately 10-20% of patients, refers to a disease course in which there is no neurological disability for at least 15 years after diagnosis. Malignant MS has a rapid progression from onset resulting in severe disability or death within a short period of time (Lublin & Reingold, 1996).

A clinically isolated syndrome (CIS) represents the first neurological episode experienced by a patient which in 30-70% of cases may develop into MS. The most common types of CIS are optic neuritis (unilateral loss of vision which usually, at least partly, resolves itself), or brainstem and spinal cord syndromes (Miller et al., 2005).

1.1.5 Expanded Disability Status Scale (EDSS)

An Expanded Disability Status Scale (EDSS) score is an objective measure of the level of neurological disability in MS (Kurtzke, 1983). The EDSS (i.e., a score between zero (no disability) and 10 (death) in 0.5 intervals) is assessed during a neurological examination. In general, the greater the EDSS score, the greater the physical disability. Eight functional systems are examined: pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral (i.e., mentation), and other. The scale is highly dependent on pyramidal tract abnormality and only slightly so on cognition. Disorders of mood and affect are not considered for the rating. This is why the Multiple Sclerosis Functional Composite (MSFC) has been proposed as a supplement to the assessment of neurological disability in MS as it places a higher emphasis on cognition (Cutter et al., 1999). This composite is made up of three tests: a timed 25 foot walk, a nine hole peg test, and the Paced Auditory Serial Addition Test (PASAT; 3 second version). A composite score is derived from the three measures.

1.1.6 Prognosis

Although there is variation in disease progression, several factors remain consistent when examined in large samples of patients. One such prediction is the time to certain disability markers, the most widely cited being the median time of progression to an EDSS score of 6.
(assistance required for walking), which ranges from 14-20 years (Weinshenker et al., 1991; Amato & Ponziani, 2000; Confavreux et al., 2000; 2003). Several factors have been associated with poorer prognosis: male gender, older age at onset, primary progressive disease course, cerebellar involvement, or motor symptoms at onset. Better prognosis is associated with a relapsing-remitting disease course, afferent nerve fiber symptoms at onset (e.g., sensory or optic neuritis), a longer time between the first and second relapse, and complete recovery after the first neurological episode (Weinshenker et al., 1991; Runmarker & Andersen, 1993; Amato & Ponziani, 2000, Myhr et al., 2001; Kantarci et al., 1998; Confavreux et al., 2003). The median survival time from disease onset is 33 years demonstrating that MS patients are at risk for premature death (Hirst et al., 2008).

### 1.1.7 Treatment

Treating MS involves several methods. Disease modifying treatments are used to reduce relapses, which, when they occur, may be managed with medication. Corticosteroids, such as methylprednisolone, are usually used to treat acute relapses; however, management of all the medical, functional, and psychosocial effects associated with the relapse is encouraged (Leary et al., 2005). Other, more chronic, symptoms associated with MS, such as fatigue, pain, or mood disorders, are also treated with various medications. Immunological disease modifying treatments are most effective in relapsing-remitting MS patients. The most common disease modifying agents are the interferon (IFN)-beta 1b (e.g., Betaseron) and 1a (e.g., Avonex and Rebif), glatiramer acetate (e.g., Copaxone), and natalizumab (e.g., Tysabri). All demonstrate a slowing of disease progression, reduction in relapse frequency and in disease activity according to brain lesions on magnetic resonance images (MRI) (IFNB Multiple Sclerosis Study Group, 1993; Paty et al., 1993; Jacobs et al., 1996; Panitch et al., 2002; Comi et al., 2001; Johnson et al., 2005; Polman et al., 2006).

### 1.2 Cognitive Impairment

Cognitive dysfunction is a common symptom of MS although it is more subtle than is seen in dementias such as Alzheimer’s disease. The most common types of cognitive deficits associated with MS are slowed information processing speed, impaired memory, and executive dysfunction (Benedict et al., 2002; Brassington and Marsh, 1998; Foong et al., 1997; Foong et al., 1999; Heaton et al., 1985). Visuospatial and verbal fluency difficulties may also be present although
less frequently (Achiron et al., 2005; Basso et al., 1996; Huber et al., 1987). The following section will discuss the most common cognitive deficits associated with MS.

1.2.1 Information Processing Speed

Speed of information processing is the most frequently impaired cognitive domain in MS. Patients who experience difficulties in this area have been shown to experience problems in all stages of the process, including automatic processing (i.e., processing that occurs without conscious effort, for example the recognition of a simple stimulus such as a letter or a number), controlled processing (i.e., processing that is conscious and requires the use of working memory), and motor programming (i.e., the automatic process that occurs when a subject prepares to carry out muscle movements) (Kujala et al. 1994).

Slowed information processing can, in part, be explained by the biological aspects that underlie the disease process. Axon demyelination contributes to a slower transfer of information between neurons. Abnormal conduction due to demyelination is cited as a possible reason for MS patients taking longer than healthy controls to complete increasingly more cognitively demanding information processing tasks (Achiron et al., 2007).

Processing speed deficits are apparent on tests such as the Paced Auditory Serial Addition Test (PASAT) which has an impairment rate of approximately 27%, and the Symbol Digit Modalities Test (SDMT) which approximately 52% of patients fail (Benedict et al., 2006). The PASAT and the SDMT are the most common tests of information processing speed for MS patients. Although the three second PASAT is currently the only cognitive index in the MS Functional Composite (MSFC), there is an emerging consensus that the SDMT may be the most sensitive and specific cognitive test for MS patients. This notion has led some researchers to suggest that it replace the PASAT in the MSFC (Brochet et al., 2008; Drake et al., 2010).

Information processing deficits are evident on computerized cognitive tests as well (Kujala et al., 1994; Wilken et al., 2003; Achiron et al., 2007; Lazeron et al., 2006; Younes et al., 2007).

1.2.2 Attention

Processing slowness may be linked to attention deficits. Tests, such as the PASAT, which assess both processing speed and attention, show that patients who are cognitively impaired give poorer
performances than cognitively intact patients and healthy controls (Kujala et al., 1995). Impaired patients had difficulty on the Stroop colour-word test as well, which is a common measure of focused attention. MS patients showed deficits in both sustained and divided attention across visual, auditory, and bimodal modalities on computerized tests of attention (McCarthy et al., 2005).

1.2.3 Memory

Although procedural memory is spared in MS, as seen in tasks such as incidental learning and priming (Grafman et al., 1991; Scarrabelotti & Carroll, 1998), patients experience problems with explicit memory, particularly working, episodic and semantic memory (Beatty et al., 1988; Benedict et al., 2003; Benedict et al., 2006; Grafman et al., 1991; Thornton & Raz, 1997). Two conflicting theories exist when it comes to determining the basis for verbal memory impairment. Problems patients tend to experience during free recall as opposed to recognition memory suggest the involvement of retrieval rather than encoding deficits (Thornton & Raz, 1997). A competing theory proposes that difficulties in acquisition rather than retrieval contribute to verbal memory impairment, whereas both acquisition and storage failure are responsible for visual memory impairment (DeLuca et al., 1998).

In keeping with the theory that memory problems associated with MS lie within the realm of information acquisition, it is not surprising that MS patients take more time to acquire information and require more trials than controls to remember the same amount of material when compared to healthy subjects (Rao, 1986; DeLuca et al., 1998). Using the Selective Reminding Test (SRT), DeLuca and colleagues (1998) were able to demonstrate that once patients acquired the necessary information over an extended number of trials (an average of seven trials versus five for healthy controls), their delayed recall was comparable to that of controls.

Working memory has been the focus of much attention in MS research since many patients experience difficulties completing tasks involving this system. According to Baddeley (2010) working memory involves manipulating information that is temporarily stored in short-term memory. The active processing of information occurs in the central executive component of working memory. The short-term storage of new information that is being manipulated occurs in the phonological loop (i.e., for auditory information) and the visuo-spatial sketchpad (i.e., for visual information). Research has shown that MS affects the normal functioning of the central
executive rather than the phonological loop which is responsible for the storage and maintenance of information (Lengenfelder et al., 2003). This deficit is evident on tasks such as the PASAT. In fact, tasks requiring patients to solely store information in short term memory without having to manipulate it show that patients perform no differently than healthy controls (Rao et al., 1984; Heaton et al., 1985).

1.2.4 Executive Function

Abstract reasoning, concept formation, and planning are constituent abilities of a process called executive function, often assessed using card sorting tasks. MS patients have been shown to experience difficulties, compared to healthy controls, on tests such as the Wisconsin Card Sorting Task (WCST), and the Delis-Kaplan Executive Function System (D-KEFS) sorting task (Rao et al., 1991a; Beatty et al., 1995; Benedict et al., 2006). Approximately 16% of patients are impaired on the D-KEFS number of correct sorts made, and 26% are impaired on the description of sorts (Benedict et al., 2006). Patients are also impaired on tests of planning ability (Foong et al., 1997; Arnett et al., 1997).

1.2.5 Visuospatial Processing

MS patients often exhibit problems relating to visual perception and spatial processing. Some patients experience difficulties with facial recognition (Beatty et al., 1989; Rao et al., 1991a). Other tests of visuospatial processing include the Judgment of Line Orientation Test (JLO) on which patients perform significantly more poorly than healthy controls (Rao et al., 1991a; Benedict et al., 2006).

1.2.6 Verbal Fluency

Verbal fluency is measured with tests such as the Controlled Oral Word Association Test (COWAT) and is often affected in MS (Benedict et al., 2006). The COWAT involves the generation of as many words as possible that fall into a certain category (e.g., words that begin with a particular letter) in a limited time. Since the test is timed, it is a measure of language as well as processing speed.
1.3 Prevalence of Cognitive Impairment

Prevalence rates of cognitive dysfunction depend on the sample examined (Duquin et al., 2008). Approximately 43-46% of patients in a community-based sample were impaired (Rao et al., 1991a; Duquin et al., 2008), compared to 59% of patients whose cognition was routinely monitored in a clinic setting, and 66% of patients who were referred due to a specific clinical problem (Duquin et al., 2008).

1.4 Correlates of Cognitive Impairment

1.4.1 Disease Duration and Course

Several studies suggest that patients with a relapsing-remitting course demonstrate less cognitive impairment than those with progressive disease (Heaton et al., 1985; Huijbregts et al., 2006; Thornton & Raz, 1997), while other studies found no such correlation (Rao et al., 1991a; Beatty et al., 1990). In a study of 108 RRMS, 71 SPMS, and 55 PPMS patients who were administered the Brief Repeatable Battery of Neuropsychological Tests (BRB-N), RRMS patients performed significantly better than SPMS patients on all tests except the Word List Generation Task (WLG), a measure of verbal fluency, (i.e., the PASAT and the SDMT (tests of information processing), the 10/36 Spatial Recall Test (a test of visuospatial processing), and the Selective Reminding Test (SRT) (a memory test)) (Huijbregts et al., 2006). RRMS patients also scored significantly better than PPMS patients on the PASAT and the SDMT but performed worse on the verbal fluency task; however, PPMS patients performed better than SPMS patients on the visuospatial processing and verbal fluency tasks. An older study showed a conflicting result: disease course was only able to predict three of the fifteen cognitive indices assessed in an extensive neuropsychological battery: short term memory, judgment of affect, and the Boston Naming Test, which was not enough to support the theory that disease course contributes to cognitive performance (Beatty et al., 1990).

Research also remains inconclusive as to whether cognitive dysfunction is related to illness duration (Heaton et al., 1985; Rao et al., 1991a). Some studies show that cognitive difficulties are detected in a large number of patients in the early stages of the disease, with approximately 45-49% of early RRMS (i.e., diagnosis made within the last three years) patients demonstrating impairment on the Brief Repeatable Battery (BRB) (Amato et al., 2010; Glanz et al., 2007;
Deloire et al., 2005). In another study where patients have not yet received a definite MS diagnosis, 27% of CIS patients were deemed impaired on the BRB (Potagas et al., 2008). On a more detailed neuropsychological assessment the CIS cognitive impairment figure jumped to 57% (Feuillet et al., 2007). These findings suggest that cognitive dysfunction can occur irrespective of disease duration. It is also unclear whether cognitive dysfunction is related to physical disability since references are contradicting (Beatty et al., 1990; Patti et al., 2009).

1.4.2 MRI Correlates

Structural and functional magnetic resonance imaging (fMRI) techniques have been used to demonstrate associations between brain pathology and cognitive dysfunction. T1 and T2 lesion load correlated significantly with global impairment as measured with the BRB or the Neuropsychological Screening Battery for Multiple Sclerosis (NPSBMS) (Lazeron et al., 2005; Mesaros et al., 2012; Akbar et al., 2010b). Failure on specific tests was also related to lesion volumes in brain regions traditionally associated with the corresponding cognitive domains: the Spatial Recall Test was correlated with lesions in the parietal lobe, and the SDMT, PASAT, and WLG were linked to frontal, parietal, and temporal lesion load (Lazeron et al., 2005).

Impairment on the PASAT and Bushke Verbal Selective Reminding Test (SRT) correlated with lesions in the frontal and parietal regions as well as total lesion volume (Sperling et al., 2001). Frontal lobe lesion load has also been associated with impaired performance on the Wisconsin Card Sorting Test which measures executive function (Arnett et al., 1994).

According to recent research, cognitive impairment is more attributable to cerebral atrophy than to lesion load (Benedict et al., 2004a; Benedict et al., 2004b; Ghaffar & Feinstein, 2007; Sánchez et al., 2008). Benedict and colleagues (2004b) demonstrated that third ventricle width is a predictor of verbal learning and verbal and non-verbal memory, and information processing speed. This finding was later replicated by Sánchez and colleagues (2008). The significance of the third ventricle lies in its inverse correlation with thalamic size. The ventricle enlargement detected in the presence of cognitive dysfunction implies atrophy of the thalamus. Brain parenchymal fraction emerged as a secondary predictor of cognitive impairment (Benedict et al., 2004b). A study that compared thalamic volume to performance on the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) showed that cognitive impairment was
correlated with atrophy of the thalamus and confirmed the significant inverse correlation of thalamic volume and third ventricle width in MS patients (Houtchens et al., 2007).

With recent advances in MRI technology, diffusion tensor imaging (DTI), which can be used to pinpoint white matter lesions that are not evident on standard MRI, have been instrumental in demonstrating significant correlations between cognitive impairment and damage to normal-appearing white matter (NAWM) and grey matter (NAGM) (Rovaris et al., 2002; Akbar et al., 2010b). Other studies have shown that the more sensitive nature of magnetization transfer (MT) imaging allows for a greater correlation between cognitive dysfunction and imaging indices in MS. A study of twenty-two patients undergoing neuropsychological assessment showed that cortical/subcortical brain magnetization transfer ratio (MTR) was associated with cognitive dysfunction (Rovaris et al., 2000). In a study of 19 patients, Cox and colleagues (2004) revealed that MTR was correlated with cognition, even when lesions were taken into account, and suggested that, as a result, cognitive impairment may act as an indicator of possible pathology in normal-appearing brain matter (NABT).

In addition to structural brain imaging research, fMRI has been used to explore neural pathways associated with cognition in MS. Working memory is a commonly examined cognitive deficit in fMRI research. Several studies have found that patients who perform normally on working memory tasks have greater activation in the regions normally involved in this function (Sweet et al., 2004; Forn et al., 2007). Another study found that patients showed less activation in the regions usually associated with working memory and more activation elsewhere, suggesting compensation occurring in the face of possible structural damage within the neural circuitry typically engaged in working memory (Wishart et al., 2004). Using the "Go/No Go" fMRI paradigm, Loitfelder and colleagues (2011) demonstrated that disease progression contributed to increased deviation from the neural circuitry activation observed in healthy controls. A study examining attention showed increased activation in the frontal cortex and posterior parietal cortex of mildly cognitively impaired patients compared to healthy controls (Penner et al., 2003). The additional activation decreased with increasing task difficulty which may suggest a ceiling effect in terms of cerebral compensation. Patients with severe cognitive impairments did not show increased cerebral activation during the attention tasks.
fMRI has also been used to visually demonstrate neurorehabilitation. Following a five-week neurorehabilitation program, patients showed increased neural activation and improved cognitive performance (Sastre-Garriga et al., 2011). Cognitive rehabilitation research together with related fMRI findings are discussed in greater detail in section 1.7.2.

1.5 Importance of Detection

Detecting cognitive difficulties in MS patients is important for a number of reasons. First, although less pronounced than the cognitive impairment seen in dementia, cognitive dysfunction in MS can nevertheless have a negative impact on patients’ quality of life, resulting in difficulties with work, social life, and other daily activities (Rao et al., 1991b). Second, driving ability can also be affected (Schultheis et al., 2001). Third, as will be discussed in section 1.7.2, findings show that training and other behavioural strategies exist to aid in enhancing cognition (Rosti-Otajärvi & Hämäläinen, 2011; Chiaravalloti et al., 2005; Goverover et al., 2011). If difficulties are not detected, clinicians cannot aid impaired patients using remedial or compensatory techniques. There are various methods of detection available.

1.6 Detecting Cognitive Impairment

1.6.1 Self-report

The Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ) is a self-administered screening questionnaire with a separate form for the patient and an informant. Each form takes approximately five minutes to complete and consists of fifteen items. Whereas the informant form correlates with patients’ objective cognitive status, as defined by neuropsychological testing, the patient form has been shown to have a stronger link with depression rather than cognitive impairment (Benedict et al., 2003). Patients’ responses were also affected by personality traits such as conscientiousness and neuroticism (Akbar et al., 2011a). These findings put into question the validity of the patient form to detect cognitive dysfunction. Compared to scores on a comprehensive cognitive evaluation, the informant MSNQ had a sensitivity of 83% and a specificity of 97% in detecting cognitive impairment (Benedict et al., 2003). An internet version of the MSNQ failed to replicate these numbers (Akbar et al., 2010a). The lack of success in this latter study could have been due to a number of reasons: first, collecting data over the internet without direct supervision may result in unreliable data, and
second, the sample had a high proportion of depressed patients, this biased sample may have contributed to a possible Type II error.

1.6.2 Mini-Mental State Examination (MMSE)

Data show that patients who are cognitively impaired often score within the normal range of the MMSE although significant differences were found between patient and control test scores (Rao et al., 1991a; Huber et al., 1987). Another study demonstrated that the MMSE was not sensitive enough to detect cognitive dysfunction at the normal cut-off score of 24; for the 56 patients tested, the false negative rate was approximately 72% (Swirsky-Sacchetti et al., 1992). When the cut-off score was raised to 27, the false negatives dropped to approximately 9% but false positives rose to an unacceptable level of approximately 30%.

1.6.3 Brief Screening Batteries

The Neuropsychological Screening Battery for Multiple Sclerosis (NPSBMS) is the most often cited brief screening battery used with MS patients (Rao et al., 1991a). The NPSBMS comprises four tests: the Selective Reminding Test (SRT) which is a verbal learning test, the 7/24 Spatial Recall Test which is a test of spatial learning, the Paced Auditory Serial Addition Test (PASAT), a measure of information processing speed and working memory, and finally, the Controlled Oral Word Association Test (COWAT), a test of verbal fluency and retrieval. This screen takes approximately 30 minutes to complete. A slightly modified version of this battery is the Rao Brief Repeatable Battery of Neuropsychological Tests (BRB-N) which consists of the aforementioned tests (with a slightly more complex spatial learning task, the 10/36, replacing the 7/24), and an additional test of information processing speed, namely, the Symbol Digit Modalities Test (SDMT) (Rao, 1990). The BRB-N has 15 alternate forms for each test except for the PASAT, which has two different versions.

A recent endeavor to create a brief screening instrument designed to tackle some of the challenges associated with assessment resulted in the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). This comprised three tests, namely the SDMT and two tests of verbal and visuospatial memory (Langdon et al., 2012; Benedict et al., 2012). The visuospatial memory test, the Brief Visuospatial Memory Test - Revised (BVMT-R), however, has a motor
component involved in testing. Sensitivity and specificity data have not yet been reported for the battery.

Although brief screening batteries have been developed with speed of administration in mind, the need for trained personnel minimizes their utility in the clinic.

1.6.4 Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS)

Recently, a new standardized battery of neuropsychological tests has been implemented for use with MS patients. A panel of experts in the field of cognitive impairment in MS has chosen a selection of seven tests to be included in The Minimal Assessment of Cognitive Function in MS (MACFIMS), a comprehensive cognitive evaluation which has subsequently been validated for use with MS patients (Benedict et al., 2002; Benedict et al., 2006). Prior to the MACFIMS there was no standardized method of defining global cognitive impairment since researchers and clinicians administered a variety of collections of tests. The MACFIMS is a 90 minute assessment and evaluates five different cognitive domains often impaired in MS patients. The SDMT and the PASAT measure speed of information processing, with the latter also including a working memory component. Learning and memory is evaluated using the California Verbal Learning Test - II (CVLT-II) and the Brief Visuospatial Memory Test - Revised (BVMT-R). The D-KEFS Sorting Test assesses executive function. Visuospatial processing is measured with the Judgment of Line Orientation Test (JLO) and verbal fluency and retrieval is evaluated with the Controlled Oral Word Association Test (COWAT). These tests are sensitive to the cognitive deficits seen in MS and will be described in detail in section 2.4.4. The authors advise the assessment of both pre-morbid IQ and depression when administering the MACFIMS. This battery is a valid and reliable method of cognitive assessment for MS patients; however it involves a great deal of time to complete, as well as expertise to administer the tests and score and interpret results. These are issues that, unfortunately, make it difficult to use regularly in the clinic.
1.7 Treatment of Cognitive Dysfunction

1.7.1 Medication

a. Disease-modifying Treatments

Cognition is not a primary outcome in clinical trials of disease modifying agents. Positive findings are few and isolated. Interferon β-1b has been shown to improve visual memory on the Wechsler Memory Scale Visual Reproduction – Delayed Recall in patients receiving a high dose (8.0 million units) between years two and four of a study conducted by Pliskin and colleagues (1996), while low-dose Interferon β-1b and placebo had no effect. Treatment with Interferon β-1b also led to more improvement on the PASAT between years three and five compared with placebo group scores (Kappos et al., 2009). Interferon β-1a also proved to have a positive impact on information processing speed and memory over a two year period when compared to placebo, a trend also suggesting improvement on measures of visuospatial processing and executive functions (Fischer et al., 2000). The authors also noted that interferon β-1a may have a protective role against decline on the PASAT over a two year period. A study assessing the effectiveness of glatiramer acetate to slow or improve cognitive decline showed no cognitive benefit (Weinstein et al., 1999). This result may, in part, be biased due to a lack of cognitive dysfunction in both treatment and placebo groups at baseline which is not representative of the MS population.

b. Cholinesterase Inhibitors

Acetylcholinesterase inhibitors such as donepezil, galantamine, and rivastigmine have been used to treat cognitive dysfunction in Alzheimer’s disease (Evans et al., 2004). Early MS research on donepezil showed promise: Greene and colleagues (2000) reported improvement in attention, memory, and executive functioning over a 12 week period in an open-pilot study. A larger, double-blind study showed improved memory as measured by the Selective Reminding Test (SRT) over a 24 week period in the donepezil group when compared to the placebo group (Krupp et al., 2004). However, a recent study with a larger sample size did not replicate these findings (Krupp et al., 2011). In the study 120 participants were given either 10 mg of donepezil or placebo, and no significant differences were found between the two groups on the primary outcome measure, the Selective Reminding Test (SRT), or the secondary outcome measures, namely other neuropsychological assessments and the clinician’s impression of memory change. This study provides definitive evidence that daily donepezil does not improve memory as
measured by the SRT in MS patients. Results from a study assessing the efficacy of rivastigmine on memory in MS reported no difference in change in memory scores between treatment and placebo groups at the end of the double-blind trial (Shaygannejad et al., 2008).

c. Amantadine

Inquiry into the effects of amantadine, an agent normally used to treat fatigue in multiple sclerosis, on cognition has been inconclusive. Geisler and colleagues (1996) have found that, in general, amantadine did not enhance cognitive performance when compared to pemoline, another fatigue medication, or placebo. However, the amantadine group demonstrated the greatest improvement on the written SDMT, which showed a significant time by medication interaction.

d. Amphetamines

Findings for amphetamines show more potential, especially for improving information processing speed. In a within-subjects study design, 19 MS patients received a placebo and three different doses of L-amphetamine separated by one-week intervals. Significantly improved PASAT and SDMT scores were seen in the highest dose of L-amphetamine (45 mg) condition (Benedict et al., 2008). In a larger study, significant cognitive improvements were seen in the L-amphetamine group on secondary outcome measures: BVMT-R total and delayed recall, as well as CVLT-II delayed recall (Morrow et al., 2009). Since no improvements were evident on the SDMT, the primary outcome measure, further research is necessary before amphetamines can be recommended as therapy.

1.7.2 Cognitive Rehabilitation and Compensation

Research remains inconclusive as to whether cognitive rehabilitation is effective in treating cognitive dysfunction. A number of factors including small sample sizes and heterogeneous methods of intervention lacking proper descriptions and often not applicable to real-world situations add to the uncertainty (das Nair et al., 2012; Rosti-Otajärvi & Hämäläinen, 2011). Although cognitive rehabilitation can involve both compensatory strategies and remediation, research has primarily focused on the latter. In a study of 40 patients with mild to moderate cognitive dysfunction randomized into one of three groups: training specific cognitive deficits, compensatory strategies, and nonspecific mental stimulation, only the group receiving specific
training exhibited a significant decrease in depression as measured by the Beck Depression Inventory (BDI); however no significant cognitive improvements except in visuo-spatial memory were detected (Jønsson et al., 1993).

A recent Cochrane review suggested that memory rehabilitation in MS may not be successful in improving memory function and cited quality limitations of studies reviewed as a possible cause for this conclusion (das Nair et al., 2012). Another study reporting minimal efficacy of cognitive rehabilitation evaluated subjective reports of cognitive impairment, mood, and quality of life of 240 patients after treatment of cognitive problems (Lincoln et al., 2002). The results revealed no beneficial effect of intervention. A double-blind randomized control trial of 82 MS patients reported no cognitive benefits of specific computerized attention and memory retraining interventions compared with training visuo-constructional and visuo-motor coordination in the control group (Solari et al., 2004).

The negative results are offset by a number of promising studies. Plohmann and colleagues (1998) showed that patients performed significantly better on a computerized attention test battery after training in that specific paradigm. In a study of 19 patients the group that completed a specific neurological training programme had significantly greater improvement on tests of executive function and spatial-constructual abilities than the group that completed only rehabilitation (e.g., occupational therapy) (Tesar et al., 2005). Computerized cognitive training has been shown to be effective in improving fatigue, working memory and mental speed in both high and low intensity training situations (Vogt et al., 2009). Similar results were observed using a different home-based computer training program where patients that adhered to the training regimen showed greater improvements in memory, information processing speed, focused attention and visuo-motor vigilance than the control group which did not complete training (Shatil et al., 2010). Other studies have also demonstrated the advantages of computerized cognitive training, with observed benefits in information processing speed, executive function, and verbal learning (Mattioli et al., 2010; Fink et al., 2010; Hildebrandt et al., 2007).

Recent cognitive rehabilitation research in the realm of memory dysfunction has shown that there are some behavioural strategies patients can use to improve memory. Although an earlier study demonstrated that simple repetition of information does not improve subsequent recall (Chiaravalloti et al., 2003), other behavioural approaches may be beneficial. A technique termed
self-generation, whereby the patient formulates his or her own concepts or words to improve learning as opposed to simply being provided with such, significantly improved recall in both patients and controls (Goverover et al., 2008). Another strategy shown to improve memory performance is spaced-learning, a technique in which learning occurs over several repeated trials with breaks in between. Spaced-learning together with self-generation was more useful than spaced learning alone in terms of enhancing recall (Goverover et al., 2011). Spaced learning on its own produced better recall than massed rehearsal.

Research involving cognitive rehabilitation and fMRI suggests that training can alter activation patterns in the brain (Penner et al., 2007; Sastre-Garriga et al., 2011; Filippi et al., 2012). Filippi and colleagues (2012) showed that cognitive training is directly associated with fMRI changes. Specifically, enhanced activity was seen in the posterior cingulate cortex (PCC) and/or precuneus and the dorsolateral prefrontal cortex (PFC) bilaterally in the treatment group when compared to baseline fMRI. Compared to a control group which received no rehabilitation, the treatment group showed significant improvements on the PASAT, the Wisconsin Card Sorting Test (WCST), and the COWAT, as well as increased activation in the dorsolateral PFC bilaterally during a Stroop interference task. These results suggest that the mechanism behind improvement on tests of information processing and executive function may be the recruitment of brain regions linked to the specific cognitive domains being trained. Baseline brain atrophy, however, may play a role in the efficacy of cognitive rehabilitation. Fink and colleagues (2010) demonstrated that brain parenchymal fraction can predict treatment outcome of an executive function intervention programme. Brain volume also seems to have an association with benefits in processing speed following cognitive training, where only the low atrophy group displayed improvement on the PASAT, but both low and high brain atrophy groups showed improvement on the CVLT (Hildebrandt et al., 2007).

Recently, there has been a number of studies supporting the theory of cognitive reserve in MS patients. Greater intellectual enrichment, defined as having engaged in enriching life activities, such as education and reading, and measured by a test of vocabulary, has been shown to be a protective factor against cognitive decline. This type of cognitive reserve can potentially mediate the effects of brain atrophy on learning and memory (Sumowski et al., 2010a). Greater premorbid cognitive leisure activity such as reading and other hobbies can have similar positive
effects on cognitive function and on the impact of existing brain atrophy on cognition (Sumowski et al., 2010b).

1.8 Limited Access to Assessment

Many patients experience difficulties obtaining a cognitive assessment from a neuropsychologist. There are several reasons why patients may encounter problems. First, a neuropsychological evaluation typically requires a referral, frequently given by a neurologist. The issue here is that approximately one third of patients do not routinely see a neurologist (Minder et al., 2008). This results in a biased population of patients being referred for cognitive testing: United States data demonstrate that patients not visiting neurologists for their MS care are more likely to be poor, have no health insurance, live in rural areas, be of African American descent, have an illness duration longer than 15 years, have difficulty walking and not using an aid, rely on a wheelchair or scooter, or be bedridden. Patients more likely to see a neurologist are female or have had a relapse in the past year (Minden et al., 2008).

Another barrier patients face in obtaining assessment is the relatively small number of neuropsychologists. Data from Canada in the last decade show that there is a total of 230 neuropsychologists and few of them are involved in MS research (Hayman-Abello BA et al., 2003). The number of neuropsychologists assessing MS patients in the clinic is unknown. The consequence of these numerous obstacles is that many patients who are in need of cognitive testing may never receive this important evaluation as part of their MS care.

1.9 Computerized Cognitive Testing

1.9.1 Advantages and Disadvantages

A potential resolution of the various issues discussed in section 1.8 can be found in computerized cognitive assessments. Since computerized testing allows for standardized administration and scoring, an expert psychometrist is not necessary which can conserve valuable time and money. Computerized tests are also ideal for tests of information processing speed since they are able to precisely measure response times (Cook et al., 2009; Wilken et al., 2003). This quality grants high reliability in tasks measuring a very common cognitive deficit in MS.
Computerized cognitive assessment for MS also has some disadvantages. First, tests requiring the use of a keyboard, mouse, or touch screen may deter patients with muscle weakness and poor upper limb coordination from completing testing. Second, computer literacy may be an issue and unfamiliarity with computers may hinder testing. Lastly, assessment of free recall or other cognitive functions requiring verbal responses could be challenging without the presence of a test administrator.

1.9.2 Existing Computerized Tests

"Paper and pencil" testing refers to tests that are not administered on the computer but rather with the use of paper, writing utensils, and other materials excluding computers and monitors to present stimuli and/or to record responses. Tests that are administered on paper but scored using a computer program (e.g., the CVLT-II) are considered "paper and pencil" tests since a computer does not need to be present during administration. Computerized tests, on the other hand, present the patient with stimuli on a computer screen and often record timed measures and score results automatically. There have been various computerized tests used with MS patients to supplement conventional "paper and pencil" testing. Computerized tests of speed of information processing have been popular for MS patients because information processing speed is a widespread deficit associated with the disease and these tests are easily scored with a computer. Often, researchers convert existing "paper and pencil" tests into a computerized format. Tests such as the Stroop (Macniven et al., 2008), the PASAT (Lengenfelder et al., 2006) and the SDMT (Akbar et al., 2011b) have all been adapted for computerized use with MS patients. With regard to the latter study, significant differences were observed between 119 MS patients and 38 healthy controls on the computerized SDMT (C-SDMT). When compared to global impairment on the BRB-N, the C-SDMT had a sensitivity of 71% and a specificity of 84% (Akbar et al., 2011b).

Computerized assessments of different stages of information processing, namely indices of motor programming, automatic, and controlled processing show that patients with mild cognitive deterioration performed significantly worse than preserved patients and controls on all stages of processing (Kujala et al., 1994). The Computerized Tests of Information Processing (CTIP) battery has been used to examine patients' performance on three different reaction time tests. The simple reaction time test measured the speed with which a participant responded to a stimulus. The choice reaction time test determined the time it took the subject to select and press one of
two keys according to the stimulus presented on the screen. Finally, during the semantic reaction task, participants were asked to decide whether a stimulus belonged to a specific semantic category (Reicker et al., 2007). Patients performed significantly worse than healthy controls on all three reaction time tests. Another study centered on attention and reaction time has also showed that patients are slower in tasks of controlled processing as well as focused, divided, and sustained attention (De Sonneville et al., 2002).

Although the majority of single computerized tests that have been used with MS patients have focused on information processing speed, one index of executive function, based on the Tower of London Task, was employed (Foong et al., 1997). This task required patients to touch the computer screen to rearrange the balls on the display. In general, patients performed worse than healthy controls on the most difficult levels but, although movement times were taken into account, the data were difficult to interpret due to the significant motor component involved.

1.9.3 Existing Computerized Batteries Used with MS Patients

In recent years, there has been an interest in developing and validating computerized batteries for patients with various neurological diseases due to the previously mentioned difficulties in obtaining conventional "paper and pencil" testing (section 1.8). Several of these validation studies have included MS patients.

a. Automated Neuropsychology Assessment Matrix (ANAM)

The Department of Defense in the United States has developed a library of computerized tests, namely the Automated Neuropsychological Assessment Matrix (ANAM), which has been used as a screening instrument for cognitive dysfunction in various populations of disease including systemic lupus erythematosus, Parkinson's disease, Alzheimer's disease, brain injury, migraines, and MS (Kane et al., 2007). A recent study of 50 RRMS patients validated selected ANAM tests for employment with MS patients (Wilken et al., 2003). Patients' results on the ANAM battery significantly correlated with a collection of conventional neuropsychological tests, and the ANAM was able to successfully distinguish between patients and healthy controls as well as cognitively impaired and intact patients. The selected tests gave measures of reaction time, working memory, information processing speed, problem solving, recognition, and fine motor speed and coordination and altogether took approximately 30 minutes to complete. Although this
particular study had no measure of reliability, a separate report of 25 healthy college students who completed five ANAM tests, four of which were used in the Wilken et al. (2003) study, showed intraclass correlation coefficients (ICCs) for each of the tests over five trials (Kaminsky et al., 2009). The following four tests appeared in the Wilken et al. (2003) study: Simple reaction time, Continuous performance test (a measure of concentration in which the participant is to decide whether a letter displayed is the same as a previous one), Math processing (a measure of information processing speed in which a participant solves a mathematical problem), and the Sternberg memory (a recognition memory task in which the participant is asked whether letters from a previous sequence appear in the following sequence). All four tests demonstrated high ICCs (≥ 0.75) which showed score stability and excellent agreement between the five repeated administrations in the healthy college student sample (Kaminski et al., 2009). Normative data for the ANAM tests can be found in Hanly et al. (2010). Although Wilken et al. (2003) were able to successfully validate the ANAM for use with MS patients, further research is warranted since the study sample was of modest size and only included RRMS patients who had minimal physical disability (i.e., mean EDSS was 2.2). The authors mentioned that upper motor coordination problems would prevent some patients from completing the ANAM because the tests require the use of a computer mouse. Absence of an executive function measure is an additional drawback of the ANAM battery.

b. Mindstreams Computerized Cognitive Battery (MCCB)

The Mindstreams Computerized Cognitive Battery (MCCB) has previously been successful in distinguishing between healthy elderly participants and those with mild cognitive impairment (Dwolatzky et al., 2004). Norms for the healthy elderly sample have been developed (Dwolatzky et al., 2004). In a recent study 58 MS patients were assessed using the Mindstreams Computerized Cognitive Battery (MCCB), a set of tests that measure information processing speed, attention, executive function, motor skills, visuospatial skills, verbal function, and memory (Achiron et al., 2007). A global cognitive index is also calculated for the tests. Although the patients performed worse than healthy controls on most measures, these data may not be generalizable to the MS population because 76% of patients had RRMS and another 17% had probable MS. Physical disability was low (i.e., mean EDSS was 2.6) and, similar to the ANAM, a motor component in the testing could possibly hinder administration or skew results. In order to interpret test scores, they must be sent over the internet to the NeuroTrax Corporation.
(NeuroTrax Corporation, 2000-2012). This transfer of test results could potentially generate concerns regarding confidentiality for patients.

c. **Amsterdam Neuropsychological Tasks (ANT)**

The Amsterdam Neuropsychological Tasks (ANT) measures focused, divided, and sustained attention, executive function, and information processing speed and takes approximately 90 minutes to complete. Data from a study of 53 MS patients and 58 healthy controls show that patients had impairments in attention and information processing speed (De Sonneville et al., 2002). Deficits in those cognitive domains were significantly correlated with disease severity (i.e., EDSS) and illness duration. The MS sample in the study examined approximately equal numbers of RRMS, SPMS, and PPMS, unlike the previous computerized testing studies discussed in section 1.9.3a and 1.9.3b. Greater disability among patients in the study (i.e., mean EDSS was 4.7) added to the applicability of the findings to the general MS population. Unfortunately, the rather modest sample size calls for additional data before the ANT can be used in the clinic. Other shortcomings of the battery itself include the necessity of using a mouse to complete testing, and the fact that the battery is too long to be used routinely in a busy clinical setting. For healthy control data, please refer to Marchetta et al. (2008).

Speed of information processing results from the ANT also correlated significantly with MRI indices, particularly slower responses were linked to brain volume reduction and higher lesion loads in the frontal and occipital lobes, adding to the construct validity of the battery (Lazeron et al., 2006).

d. **Cognitive Stability Index (CSI)**

The Cognitive Stability Index (CSI) was designed to screen for cognitive impairment in patients with various neurological diseases and generally has an administration time of approximately 30 minutes. The battery assesses attention, information processing speed, visual memory, and reaction time. Using the CSI Younes and colleagues (2007) examined 40 MS patients and compared results to test scores from a comprehensive neuropsychological battery as well as the PASAT on its own. The CSI was found to be more sensitive than the PASAT alone (i.e., 83% versus 28% sensitivity) and equal in specificity (i.e., 86%) in detecting cognitive impairment as defined by the neuropsychological battery. The sample consisted of mostly RRMS patients and
EDSS scores were not given for the sample which makes it difficult to interpret and generalize the findings. Although reliability was not measured in this particular study, other data demonstrate satisfactory test-retest reliability for CSI test results in patients with traumatic brain injury, attention deficit/hyperactivity disorder, and Alzheimer's disease: attention $r = 0.73$, information processing speed $r = 0.73$, visual memory $r = 0.68$, and reaction time $r = 0.80$ (Erlanger et al., 2002). Normative data can also be found in Erlanger et al. (2002). The CSI is administered over the internet which could pose possible reliability concerns due to lack of professional supervision. This has been demonstrated in the failed validation attempt of the computerized MSNQ administered over the internet absent supervision (Akbar et al., 2010a). Similar to previously discussed computerized assessments, a motor component is involved in the testing process (i.e., patients respond by pushing a number key), a task that could be difficult for more disabled patients.

e. Cognitive Drug Research (CDR) Battery

The Cognitive Drug Research (CDR) battery may be the quickest computerized assessment currently validated for use with MS patients. This 15-20 minute assessment evaluates five separate cognitive domains: attention, vigilance, working memory, episodic memory, and information processing speed. A composite score is derived from the mean of the completed tests. The CDR may be a viable substitute for the BRB-N and the MACFIMS in clinical and research settings where time constraints and expertise might prohibit routine testing. In a study of 43 RRMS patients who completed the CDR, the PASAT, and the Digit Symbol Substitution Test (DSST), the CDR composite score was significantly correlated with each test (Edgar et al., 2011). High correlations were also found between the CDR and EDSS scores ($r = 0.61$). With the exception of working and episodic memory, all other CDR indices had good test-retest reliability ($r > 0.7$) over successive assessments, especially the composite score ($r \geq 0.9$). Another benefit of the CDR is the minimal motor component involved in testing. In place of having to use a keyboard or mouse, patients are provided with a response box with two large buttons for "YES" and "NO". Unfortunately, several study limitations currently prevent the CDR from being implemented as a screening tool in clinics. The modest sample size, paired with the fact that only RRMS patients with minimal disability were assessed (i.e., mean EDSS was 2.8) calls for additional validation. Another drawback of the study was the absence of a gold standard battery validated for use with MS patients with which the CDR could be compared. Finally, the
necessity of an administrator during testing to record verbal responses is another potential disadvantage of the battery.

f. **Computerized Attention Test Battery (TAP)**

The computerized attention battery (TAP) is a collection of five attention tests: alertness, go/no go, flexibility, divided attention, and working memory, all of which are reaction time tasks with various degrees of complexity. In a study of 21 MS patients and 22 healthy controls, all TAP subtests successfully distinguished patients from controls, with patients performing slower than controls on the reaction time tests (Schulz et al., 2006). A comparison with the comprehensive neuropsychological battery that was used in the study was not made. Additional validation comes from an fMRI study that examined brain activation during three of the five TAP tests in 14 MS patients and seven healthy controls (Penner et al., 2003). Data show that mildly impaired patients displayed increased activation compared to controls in the frontal and posterior parietal cortices. This enhanced activation decreased with task complexity, a phenomenon previously described in section 1.7.2 which suggests a limit of cerebral compensation as task difficulty increases.

1.9.4 **Future Directions**

Computerized cognitive assessment in MS has seen promising advances in recent years and may be key in offering patients more accessible cognitive testing. Although data from the few studies have been limited by modest sample sizes predominately consisting of RRMS patients with minimal physical disability, and computerized tests have not been perfected to entirely exclude motor components from testing, existing studies show great potential. All computerized assessments were successful in distinguishing between MS patients and healthy controls. Future research should focus on eliminating motor confounders that could hinder testing, increase sample size, and consider neurological variables that could influence test results such as disease course and EDSS when recruiting study participants. Data on reliability as well as discriminant and ecological validity should also be reported.

1.10 **Aim**

The primary aim of the present study is to validate a new computer generated cognitive screening battery in a representative sample of MS patients. A secondary aim is to ensure that the battery requires minimal time and expertise to administer, and limited motor ability to complete.
1.11 Rationale

Cognitive dysfunction affects approximately half of MS patients and many individuals who require an assessment do not receive one due to certain barriers. Reasons preventing patients from obtaining cognitive testing range from not having access to a neurologist who can make a referral for neuropsychological evaluation to the limited number of neuropsychologists available to perform testing. The long administration times, the special expertise required, and the related expense of testing (in private practice settings) can make cognitive testing unattainable as part of a routine clinical assessment.

A short semi-automated computerized assessment could eliminate the need for an experienced psychometrist to perform testing, and would allow for instant scoring of cognitive results, consequently lowering the time and cost of administration. The minimal demand placed on motor ability within some of the computerized tests would allow patients who have more disabling, progressive disease to complete testing as well. While not meant to replace detailed, conventional neuropsychological inquiry, computerized testing could fill a gap in existing research and potentially allow for rapid, valid and reliable assessment in busy neurological outpatient clinics.
Chapter 2
Methods

2.1 Participants

2.1.1 Patients

a. Inclusion criteria

Inclusion criteria for patients were a confirmed diagnosis of MS (according to the revised McDonald criteria, Polman et al., 2005), and ages between 18-65 years. Patients were recruited if they had relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), or primary progressive MS (PPMS).

b. Exclusion criteria

Patients were excluded if they did not have visual acuity of at least 20/100 in one eye or were colour blind, had a serious physical or psychiatric illness (including substance abuse), had a history of traumatic brain injury, had a learning disability, or had another neurological disease other than MS. Patients who had done neuropsychological testing in the past year were also excluded.

c. Sample

One hundred and eleven patients were entered into the study. Twelve patients were excluded from the analysis due to one of the following reasons: unconfirmed diagnosis of MS (N = 2), learning disability (N = 2), marked dysarthria (N = 1), previous head injury (N = 1), severe fatigue (N = 1), severe physical disability (N = 3), visual acuity below 20/100 in both eyes (N = 1), and stroke (N = 1). The final sample consisted of 99 MS patients (ages 22 to 63 years). No patient had dementia or psychosis.

2.1.2 Healthy Controls

a. Inclusion criteria

Healthy participants were included if they were between the ages of 18-65.
b. Exclusion criteria

Exclusion criteria for healthy participants were the same as for patients.

c. Sample

Ninety-nine healthy controls, comparable in age, gender, education, and premorbid IQ to the MS patients, were enrolled in the study. One control was excluded from the analysis due to dyslexia, for a final sample size of 98 healthy subjects.

2.2 Recruitment

2.2.1 Sunnybrook Health Sciences Centre

Study flyers were posted at Sunnybrook Health Sciences Centre for both patients and healthy controls. Patients were recruited from two different Sunnybrook MS clinics. Patients were given flyers for the study during their clinical visit and were given information about the study by their treating physician (either psychiatrist or neurologist). Interested patients contacted study personnel by telephone and were given a more detailed explanation of what the study entailed. At this point, patients decided whether they wished to participate. Another method of recruitment involved using a patient database to contact patients meeting inclusion criteria by telephone.

2.2.2 St. Michael’s Hospital Multiple Sclerosis Clinic

Patients were also recruited at St. Michael's Hospital. Study flyers for both patients and healthy controls were posted at the St. Michael's MS Clinic. Patients were also given flyers during their regular clinical visit and were told about the study by their treating physician (neurologist). Flyers were also distributed to patients and their families in the waiting room.

2.2.3 Craigslist and Kijiji

Ads were posted on both Craigslist and Kijiji to recruit healthy volunteers. Interested volunteers contacted study personnel by telephone.

2.2.4 Payment

All participants were reimbursed for parking and transportation. Patients were offered the option to receive their cognitive test results.
2.3 Ethics

The study received approval from the Research Ethics Boards of both Sunnybrook Health Sciences Centre and St. Michael’s Hospital. Informed consent was obtained from all participants.

2.4 Data collection

2.4.1 Demographics

Demographics questionnaires were administered to both patients and healthy controls prior to cognitive assessment. Data collected included age, gender, years of education, employment status and marital status.

2.4.2 Neurological data

The patients' demographic questionnaire also included items pertaining to disease related data. Variables such as disease course, illness duration, and Expanded Disability Status Scale (EDSS) were collected. EDSS scores were obtained from the patients' neurologists.

2.4.3 Visual acuity and colour blindness

Visual acuity and colour recognition were measured using the Snellen near vision eye chart to determine whether patients fit the inclusion criteria. Patients were asked to read the letters with one eye at a time while the chart was held 14 inches away. Patients with visual acuity below the threshold of 20/100 in both eyes were excluded from the study.

2.4.4 Cognitive assessment

a. Computerized cognitive assessment battery

The full computer generated battery included five tests of speed of information processing and working memory: (i) the Stroop Colour-Word Test (STROOP), (ii) the Computerized Symbol Digit Modalities Test (C-SDMT), (iii) the Paced Visual Serial Addition Test (4 second and 2 second trials (PVSAT-4, PVSAT-2), (iv) the Simple Reaction Time test (SRT), and (v) the Choice Reaction Time test (CRT). Screenshots for each computerized test are shown in Figures 1-5. An extra measure, namely (vi) the Choice Reaction Time minus the Simple Reaction Time (CRT-SRT), is also described. The tests are run on Windows software with no additional hardware needed for administration. A test administrator reads the instructions for each test
aloud to the subject and then starts the test. Verbal responses for the STROOP, C-SDMT, and PVSAT are recorded by the administrator.

i. Stroop Colour-Word Test (STROOP)

The Stroop Colour-Word Test (STROOP) is a computerized version of the classic Stroop task (Stroop, 1935) which measures the total time to complete an interference task in which the patient is asked to pay attention to one attribute of a stimulus while ignoring another. The patient is first instructed to read a list of words (i.e., names of colours) that are presented on the computer screen. The second trial entails naming the colours of squares presented on the screen. During the final trial, the patient is presented with the names of colours written in different colours and is asked to indicate the colour of the words and not the names of the words. Responses are given orally. Errors are recorded by the tester. Each trial is timed by the computer. The administrator begins and ends each trial by hitting the space bar. The time a patient takes to complete the distraction task is recorded as the raw score for the test. A screenshot for the Stroop is shown in Figure 1.

Figure 1. Screenshot of the Stroop Colour-Word Test
ii. **Computerized Symbol Digit Modalities Test (C-SDMT)**

The Computerized Symbol Digit Modalities Test (C-SDMT) is a computerized adaptation of the common SDMT (Smith, 1982). This test measures information processing speed. The display on the screen includes a legend with nine boxes of symbols underneath the numbers one through nine, each number corresponding to a different symbol. Below the legend there is another nine boxes with the same symbols mixed in a different order. The patient is instructed to say verbally, as quickly as possible, the number corresponding to each symbol until completing the row of nine symbols. A practice trial of nine symbols is given before beginning the test. The test consists of eight trials. At the end of each trial the administrator strikes the space bar for the next trial to automatically begin. The administrator records the number of errors made per trial. The time to complete each trial of nine symbols is measured automatically by the computer which also gives the total and mean time per trial. The mean time to complete each trial is used as a raw score for this measure.

The method of assessment for the C-SDMT is different from that of the paper and pencil SDMT in that the SDMT measures the number of correct matches in 90 seconds. In the C-SDMT patients are expected to complete all eight trials of the test and their raw score consists of the time this takes to complete. In doing this, the computerized task does not have a full screen of symbols so patients are not forced to move their head and eyes up and down the screen (or paper) which reduces the motor component associated with the test. Although the time to complete the computerized test is unrestricted, the mean (SD) administration (excluding instructions) was only 128.5 (36.2) seconds. A screenshot for the C-SDMT is shown in Figure 2.
iii. Paced Visual Serial Addition Test (PVSAT)

The Paced Visual Serial Addition Test (4 second and 2 second trials (PVSAT-4, PVSAT-2)) is a visual version of the PASAT (Gronwall, 1977). In this test a series of numbers between one and nine appear one at a time on the screen and patients are asked to add the number that they see to the previous number seen and state the sum aloud. In the four second trial (PVSAT-4), numbers are shown every four seconds, and in the two second trial (PVSAT-2), every two seconds. Correct responses are recorded by the tester and summed at the end of each trial. There are a total of 30 numbers per trial and the number of correct responses for each of the two trials is used as a raw score. Up to three practice trials are available before commencing the test. A screenshot for the PVSAT is shown in Figure 3.
iv. Simple Reaction Time (SRT)

The Simple Reaction Time (SRT) test measures the speed with which a patient reacts to a simple stimulus. Three empty squares are shown on the screen. An arrow pointing to the right appears in the middle square. The square on the right turns yellow either simultaneously with the arrow or shortly after. The task entails the patient pressing a key with a single digit on their right hand, as quickly as possible, when the right square turns yellow. The SRT comprises 20 trials for the right hand, and the interval between the arrow appearing and the square turning yellow alternates randomly between 0, 200, 800, and 1600 milliseconds, each interval occurring five times per trial. The different intervals aim to reduce any anticipatory responses. A practice trial is given for the right hand. This task is repeated with the left hand using the left square as the stimulus. Reaction time is recorded by the computer. The raw score for this test is the mean reaction time for both hands. A screenshot for the SRT is shown in Figure 4.
v. Choice Reaction Time (CRT)

The Choice Reaction Time (CRT) test is similar in appearance to the SRT only, here, the patient is instructed to use both hands for the trial. Again, three squares are presented on the screen. When the arrow in the middle square points to the right, the right square turns yellow, and the patient is asked to press a designated key with the right hand. The same procedure is followed for the left side. An added element in this test is a cross that sometimes appears in the place of the arrow in the middle square. In this instance, it is not evident whether the right or left square will turn yellow, but the patient is asked to follow the same process regardless of whether the trial is cued (arrow) or warned (cross). A total of 80 trials constitute the test: 40 cued and 40 warned. The intervals between the arrow or cross and the square turning yellow are the same as those in the SRT. There is a practice trial before the test begins. The raw score is made up of the mean reaction time for both hands for all trials (i.e., cued and warned). A screenshot for the CRT is shown in Figure 5.
vi. Choice Reaction Time minus Simple Reaction Time (CRT-SRT)

The Choice Reaction Time minus Simple Reaction Time (CRT-SRT) index is not a test but a measure of cognitive speed. By subtracting the time for the SRT from that of the CRT a mental component of speed is obtained.

b. Computerized Test Failure

A score more than 1.5 standard deviations below the mean of normative scores derived from the healthy control sample constituted a failed score on each computerized test. No patients were incapable of completing the computer generated tests due to cognitive impairment.

c. Minimal Assessment of Cognitive Function in MS (MACFIMS)

The gold standard with which the computerized assessment is compared is a conventional comprehensive neuropsychological assessment. The MACFIMS is a battery of neuropsychological tests developed for use with MS patients by expert consensus (Benedict et al., 2006). Published normative data exist for each test and these were used for scoring in this study. The MACFIMS consists of seven tests which measure the following five cognitive
domains: (i) speed of information processing, (ii) verbal and visual learning and memory, (iii) executive function, (iv) visuospatial processing, and (v) verbal fluency.

i. Speed of information processing

01. Paced Auditory Serial Addition Test (PASAT)

The Paced Auditory Serial Addition Test (PASAT) consists of two separate trials (Gronwall, 1977). Trial one (PASAT-3) is the three second version and trial two (PASAT-2) is the two second version. The PASAT has a working memory component in addition to measuring information processing speed. In this test patients must listen to a series of 60 numbers between one and nine. Patients are to add the number they hear with the previous number heard and not to the cumulative total. In the first and easier trial, the numbers are presented every three seconds, in the second, every two seconds. The number of correct responses corrected for years of education constitutes the raw score.

02. Symbol Digit Modalities Test (SDMT)

In the Symbol Digit Modalities Test (SDMT) patients are given a paper with a symbol and number legend on the top, with nine numbers corresponding to nine different symbols (Smith, 1982). Below are rows of symbols and patients are asked to say, aloud, the number that corresponds to each consecutive symbol. The number of correct responses given in a span of 90 seconds, corrected for age and years of education, constitutes the raw score.

ii. Verbal and visual learning and memory

01. California Verbal Learning Test – II (CVLT-II)

The California Verbal Learning Test - II (CVLT-II) consists of both an immediate total recall and a delayed recall trial. In the immediate recall trial, a list of 16 words is read to the patient five times (Delis et al., 2000). The total number of correct words recalled during these five administrations is recorded. For the delayed recall trial patients are asked to recall the words twenty minutes after initial test administration.
02. Brief Visuospatial Memory Test – Revised (BVMT-R)

The Brief Visuospatial Memory Test - Revised (BVMT-R) also has an immediate total recall and a delayed recall trial. In this test patients are presented with a display of six figures for ten seconds (Benedict et al., 1996; Benedict, 1997). Once the display is taken away, patients are asked to draw the figures as accurately as possible and in the correct location on the page. This procedure is done three times. Drawings for each trial are scored according to accuracy of both the drawing and the location and summed for a total recall score. Twenty minutes after initial administration patients are asked to once again draw the figures without seeing the display. These drawings are scored for delayed recall.

iii. Executive Function

01. D-KEFS Sorting Test

The D-KEFS Sorting Test is a card sorting task in which patients are asked to sort six cards into two groups of three cards and explain the rationale behind the sort (Delis et al., 2001). Cards in each group must be the same in some way. The task is scored according to the number of correct sorts patients make and the description patients provide for their sorts.

iv. Visuospatial processing

01. Judgment of Line Orientation (JLO)

In the Judgment of Line Orientation (JLO) test, patients are to identify the orientation of two lines presented on a piece of paper (Benton et al., 1994). These lines can have one of 11 different orientations and patients are to specify the number of each orientation according to an orientation legend, also displayed in front of them. The number of correct responses out of 30, corrected for age and gender, represents the raw score.

v. Verbal fluency

01. Controlled Oral Word Association Test (COWAT)

In the Controlled Oral Word Association Test, patients are asked to say as many words as they can think of that begin with a certain letter (Benton & Hamsher, 1989). Three letters are used in the test and one minute is provided for responses for each letter. The total number of responses for the three trials, corrected for years of education and gender, constitutes the raw score.
d. MACFIMS Test Failure

Failure on each test was defined as a score more than 1.5 standard deviations below the mean of normative values, as specified in the MACFIMS validation study (Benedict et al., 2006). Global impairment was defined as failure on two or more cognitive measures.

2.4.5 Order of Testing

The order of presenting the tests had the potential to bias results. Administering the MACFIMS first would introduce practice effects into the C-SDMT and PVSAT. The full computer generated battery is also much shorter (20 minutes) than the MACFIMS (90 minutes) so administering it first would limit the effects of fatigue that could ensue if administered second. A third key reason for administering the computerized tests first was that the healthy participants were not administered the MACFIMS. For these reasons, a larger portion of patients (74) were administered the computer generated screening measure first.

On the other hand, the advantage of administering the MACFIMS first was to eliminate practice effects for the PASAT and the SDMT, factors that could bias the overall criterion measure. To investigate these competing influences, 25 patients were administered the MACFIMS first.

2.4.6 Premorbid IQ

Premorbid IQ was assessed using the American National Adult Reading Test (ANART) (Grober & Sliwinski, 1991). Patients were asked to pronounce 50 words. The number of errors was used to derive an estimated verbal IQ score.

2.4.7 Depression and Anxiety

Depression and anxiety in both patients and healthy controls were measured using the Hospital Anxiety and Depression (HAD) Scale (Zigmond & Snaith, 1983). This scale was chosen as it has been validated for use with MS patients (Honarmand & Feinstein, 2009). The scale consists of 14 items (seven for depression and seven for anxiety) which probe self-reported mood within the week prior to testing. Each item is scored from 0-3 for a total of 21 points for each subscale and has a cut-off point of 8.0 indicating clinically significant depression and anxiety (Honarmand & Feinstein, 2009). Thus, patients were deemed depressed if they had scored 8.0 or more points on
the depression portion of the scale, and anxious if they received 8.0 or more on the anxiety questions.

2.4.8 Test-retest reliability

Of the 169 participants, 49 (30 patients and 19 healthy controls) returned to complete a retest of the computer generated battery approximately 71.7 (SD = 26.2) days after initial testing. None of the patients had relapses during the time between the first and second test administration.

2.5 Statistical analysis

The Kolmogorov-Smirnov test was used to determine whether the scores for each semi-automated computerized test were normally distributed. T-tests or Mann-Whitney U tests were then conducted on each test to compare healthy control and MS patient scores. Patients were then split into two groups, those impaired and those intact on the MACFIMS. One-way ANOVAs or Kruskal-Wallis tests were used to compare computerized test results of MS patients impaired on the MACFIMS to those who were not impaired and healthy controls. Cut-off scores to determine impairment for the computerized tests were derived from the healthy control sample. Patients scoring more than 1.5 SD below the mean of normative scores for each test were deemed to have failed that particular test. Impairment rates for each computerized test were calculated.

Impairment on the MACFIMS served as the "gold standard" for cognitive dysfunction. Failure on two out of 11 measures was deemed to represent overall cognitive impairment. The results of the computerized tests were compared to those of the MACFIMS. Sensitivity and specificity values were calculated for each threshold of impairment on the computerized screen as compared to global impairment on the MACFIMS. Thereafter, combinations of computerized tests were sought to create a more sensitive and specific battery. Beginning with the single most sensitive test and adding to it the test with the second highest rate of impairment, each new combination was compared to global impairment on the MACFIMS, until an ideal sensitivity and specificity were reached.

A receiver operating characteristic (ROC) analysis was then undertaken to assess which threshold on the computerized battery gave the best yield with respect to cognitive impairment as defined by MACFIMS global impairment. Pearson r correlations were conducted to assess the association between the computerized tests used in the final battery and the conventional tests.
from which they are derived. Finally, a logistic regression analysis was performed to rule out potential confounders of cognitive impairment on the computerized screen. The variables age, gender, education, EDSS score, illness duration, depression, anxiety, and premorbid IQ were included in the logistic regression analysis.

Test-retest reliability of the computer generated screen was assessed using Kappa Intraclass correlation coefficients (ICC).
Chapter 3
Results

3.1 Demographic and disease related data

Demographic comparisons between MS patients and healthy control subjects are shown in Table 1 and were not significantly different. Neurological data for patients are also presented in Table 1.

Table 1. Demographic and disease characteristics of MS patients (N=99) and healthy controls (N=98)

<table>
<thead>
<tr>
<th></th>
<th>MS Patients (N = 99)</th>
<th>Healthy Controls (N = 98)</th>
<th>t-test / $x^2$</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>48.5 (9.7)</td>
<td>46.4 (9.0)</td>
<td>t = -1.6</td>
<td>p = 0.108</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>67 (67.7%)</td>
<td>64 (65.3%)</td>
<td>$x^2 = 0.124$</td>
<td>p = 0.724</td>
</tr>
<tr>
<td>Premorbid IQ</td>
<td>112.9 (8.2)</td>
<td>114.1 (8.0)</td>
<td>t = 1.0</td>
<td>p = 0.316</td>
</tr>
<tr>
<td>Years of education</td>
<td>14.8 (2.2)</td>
<td>15.1 (1.6)</td>
<td>t = 1.2</td>
<td>p = 0.251</td>
</tr>
<tr>
<td>Illness duration (yrs)</td>
<td>11.6 (8.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDSS</td>
<td>4.1 (2.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease course</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RRMS</td>
<td>44 (44.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPMS</td>
<td>38 (38.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPMS</td>
<td>17 (17.2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EDSS: Expanded Disability Status Scale; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis
3.2 Cognitive data

3.2.1 MACFIMS

Based on the MACFIMS determined threshold (at least two failed tests out of 11 indices), 42 (42.4%) MS patients were deemed cognitively impaired. Table 2 shows the impairment rate of each test for RRMS, SPMS, and PPMS patients, as well as for the total MS sample.

Table 2. MACFIMS tests impairment rate

<table>
<thead>
<tr>
<th>Test</th>
<th>RRMS (N = 44)</th>
<th>SPMS (N = 38)</th>
<th>PPMS (N = 17)</th>
<th>Total MS (N = 99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDMT</td>
<td>41.9</td>
<td>50.0</td>
<td>52.9</td>
<td>46.5</td>
</tr>
<tr>
<td>PASAT-2</td>
<td>22.7</td>
<td>38.9</td>
<td>25.0</td>
<td>28.3</td>
</tr>
<tr>
<td>PASAT-3</td>
<td>18.2</td>
<td>32.4</td>
<td>25.0</td>
<td>24.2</td>
</tr>
<tr>
<td>BVMT-DR</td>
<td>9.3</td>
<td>42.1</td>
<td>17.6</td>
<td>23.2</td>
</tr>
<tr>
<td>BVMT-TOT</td>
<td>7.0</td>
<td>36.8</td>
<td>17.6</td>
<td>20.2</td>
</tr>
<tr>
<td>CVLT-DR</td>
<td>13.6</td>
<td>21.1</td>
<td>23.5</td>
<td>18.2</td>
</tr>
<tr>
<td>COWAT</td>
<td>15.9</td>
<td>18.4</td>
<td>17.6</td>
<td>17.2</td>
</tr>
<tr>
<td>CVLT-TOT</td>
<td>4.5</td>
<td>18.4</td>
<td>11.8</td>
<td>11.1</td>
</tr>
<tr>
<td>D-KEFS DS</td>
<td>2.3</td>
<td>13.2</td>
<td>23.5</td>
<td>10.1</td>
</tr>
<tr>
<td>JLO</td>
<td>13.6</td>
<td>7.9</td>
<td>0.0</td>
<td>9.1</td>
</tr>
<tr>
<td>D-KEFS SS</td>
<td>0.0</td>
<td>10.5</td>
<td>11.8</td>
<td>6.1</td>
</tr>
</tbody>
</table>

3.2.2 Computer generated tests

a. Comparisons between MS patients and healthy controls

Comparisons between MS patients and control subjects on the computer generated cognitive tests are shown in Table 3. The data revealed significant differences for all the indices. All the computerized tests successfully distinguished between MS patients and healthy controls. Significant differences were also found in depression and anxiety, indicating that patients were both more depressed and more anxious than healthy controls, although means did not exceed the threshold of 8.0 for either depression or anxiety.

Table 3. Comparison of Computerized Test Scores and HAD scores for MS patients and healthy controls

<table>
<thead>
<tr>
<th>Computerized Test</th>
<th>Healthy Controls</th>
<th>MS Patients</th>
<th>t-test / Mann-Whitney U</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>STROOP (seconds)</td>
<td>26.6 (8.5)</td>
<td>30.7 (11.1)</td>
<td>t = -3.0</td>
<td>0.003</td>
</tr>
<tr>
<td>C-SDMT (seconds)</td>
<td>12.8 (2.3)</td>
<td>16.1 (4.5)</td>
<td>t = -6.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PVSAT-4 (number correct)</td>
<td>28.6 (2.2)</td>
<td>26.2 (5.1)</td>
<td>U = 3517.5</td>
<td>0.002</td>
</tr>
<tr>
<td>PVSAT-2 (number correct)</td>
<td>24.5 (5.2)</td>
<td>20.9 (6.5)</td>
<td>U = 3198.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SRT (milliseconds)</td>
<td>393.6 (118.0)</td>
<td>445.4 (141.2)</td>
<td>t = -2.7</td>
<td>0.007</td>
</tr>
<tr>
<td>CRT (milliseconds)</td>
<td>444.0 (88.8)</td>
<td>543.5 (160.6)</td>
<td>t = -5.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CRT - SRT (milliseconds)</td>
<td>52.5 (86.2)</td>
<td>99.5 (89.6)</td>
<td>t = -3.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HAD-Depression</td>
<td>2.4 (3.0)</td>
<td>6.9 (4.0)</td>
<td>t = -8.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HAD-Anxiety</td>
<td>4.6 (3.1)</td>
<td>7.2 (4.5)</td>
<td>t = -4.5</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

STROOP: Stroop Colour-Word Test; SDMT: Computerized Symbol Digit Modalities Test; PVSAT: Paced Visual Serial Addition Test (4 second and 2 second versions); SRT: Simple Reaction Time Test; CRT: Choice Reaction Time Test; CRT-SRT: Choice Reaction Time minus Simple Reaction Time; HAD: Hospital Anxiety and Depression Scale
b. Comparisons between MS patients impaired and intact on the MACFIMS and healthy controls

The results of a three-way comparison of the computer generated cognitive data are shown in Table 4. They revealed significant differences in every computerized test between the cognitively impaired MS patients on the one hand, and the cognitively intact patients and healthy controls on the other. The only measure that failed to show a significant difference between impaired and intact patients was the CRT-SRT. In addition, the cognitively intact MS patients were also found to be more impaired than the healthy controls on one computerized test, the CRT, and, by extension, the CRT-SRT.

c. Impairment rates

Results from each semi-automated computerized test were dichotomized (intact versus impaired) relative to the healthy control data. Scores more than 1.5 SD below the mean of normative data were deemed impaired. Table 5 shows the impairment rate of the computerized tests based on this cut-off score for RRMS, SPMS, and PPMS patients, as well as for the total MS sample. The C-SDMT emerged as the most frequently impaired index followed by the PVSAT-4.

d. Sensitivity and specificity analysis

Sensitivity and specificity were first established for the entire computer generated battery as compared to MACFIMS global impairment. The impairment threshold of the computerized battery was alternatively set to 1/7, 2/7, 3/7, etc., tests impaired. Table 6a shows the sensitivity and specificity for each threshold of the computerized battery when using MACFIMS global impairment as the gold standard. Failure on at least one test out of seven on the semi-automated computerized battery yields the highest sensitivity (i.e., 83.3%) although it is accompanied by a lower specificity (i.e., 68.4%).

An alternate approach was taken in which the computerized tests were individually selected based on their rate of impairment. In this manner, the C-SDMT was examined on its own against MACFIMS global impairment. The PVSAT-4 was subsequently added to the C-SDMT and the analysis was repeated. The remainder of tests in decreasing order of sensitivity were added. The results can be seen in Table 6b. The best combination of tests proved to be the C-SDMT, PVSAT-4 and PVSAT-2. Failure on at least one of these three tests gave a sensitivity of 83.3%
Table 4. Comparing MACFIMS Intact, Impaired, and Healthy Controls on Computerized Test Scores

<table>
<thead>
<tr>
<th>Test</th>
<th>Impaired Mean (SD) (N = 42)</th>
<th>Intact Mean (SD) (N = 57)</th>
<th>HC Mean (SD) (N = 98)</th>
<th>F / χ²</th>
<th>p</th>
<th>Impaired vs. Intact</th>
<th>Impaired vs. HC</th>
<th>Intact vs. HC</th>
</tr>
</thead>
<tbody>
<tr>
<td>STROOP (seconds)</td>
<td>36.4 (13.0)</td>
<td>26.6 (7.0)</td>
<td>26.6 (8.5)</td>
<td>F = 18.6</td>
<td>&lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p = 1.000</td>
</tr>
<tr>
<td>C-SDMT (seconds)</td>
<td>18.9 (5.2)</td>
<td>14.0 (2.3)</td>
<td>12.8 (2.3)</td>
<td>F = 56.0</td>
<td>&lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p = 0.070</td>
</tr>
<tr>
<td>PVSAT-4 (number correct)</td>
<td>22.7 (5.8)</td>
<td>28.6 (2.7)</td>
<td>28.6 (2.2)</td>
<td>χ² = 40.4</td>
<td>&lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p = 0.836</td>
</tr>
<tr>
<td>PVSAT-2 (number correct)</td>
<td>16.0 (5.3)</td>
<td>24.3 (4.8)</td>
<td>24.5 (5.2)</td>
<td>χ² = 49.7</td>
<td>&lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p = 0.728</td>
</tr>
<tr>
<td>SRT (milliseconds)</td>
<td>498.3 (173.7)</td>
<td>408.9 (100.0)</td>
<td>393.6 (118.0)</td>
<td>F = 9.6</td>
<td>&lt; 0.001</td>
<td>p = 0.003</td>
<td>p &lt; 0.001</td>
<td>p = 0.754</td>
</tr>
<tr>
<td>CRT (milliseconds)</td>
<td>609.0 (182.1)</td>
<td>499.1 (127.8)</td>
<td>444.0 (88.8)</td>
<td>F = 24.0</td>
<td>&lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p = 0.025</td>
</tr>
<tr>
<td>CRT-SRT (milliseconds)</td>
<td>110.7 (76.2)</td>
<td>91.8 (97.7)</td>
<td>52.5 (86.2)</td>
<td>F = 7.2</td>
<td>0.001</td>
<td>p = 0.563</td>
<td>p = 0.002</td>
<td>p = 0.025</td>
</tr>
</tbody>
</table>

STROOP: Stroop Colour-Word Test; C-SDMT: Computerized Symbol Digit Modalities Test; PVSAT: Paced Visual Serial Addition Test (4 second and 2 second versions); SRT: Simple Reaction Time Test; CRT: Choice Reaction Time Test CRT-SRT: Choice Reaction Time minus Simple Reaction Time
Table 5. Computerized tests impairment rate

<table>
<thead>
<tr>
<th>Test</th>
<th>RRMS (N = 44)</th>
<th>SPMS (N = 38)</th>
<th>PPMS (N = 17)</th>
<th>Total MS (N = 99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-SDMT</td>
<td>31.8</td>
<td>36.8</td>
<td>41.2</td>
<td>35.4</td>
</tr>
<tr>
<td>PVSAT-4</td>
<td>27.3</td>
<td>22.2</td>
<td>6.2</td>
<td>21.2</td>
</tr>
<tr>
<td>PVSAT-2</td>
<td>15.9</td>
<td>22.2</td>
<td>25.0</td>
<td>19.2</td>
</tr>
<tr>
<td>CRT</td>
<td>22.7</td>
<td>22.2</td>
<td>7.1</td>
<td>19.2</td>
</tr>
<tr>
<td>CRT-SRT</td>
<td>18.2</td>
<td>25.7</td>
<td>14.3</td>
<td>19.2</td>
</tr>
<tr>
<td>STROOP</td>
<td>6.8</td>
<td>13.2</td>
<td>23.5</td>
<td>12.1</td>
</tr>
<tr>
<td>SRT</td>
<td>13.6</td>
<td>11.4</td>
<td>7.1</td>
<td>11.1</td>
</tr>
</tbody>
</table>

C-SDMT: Computerized Symbol Digit Modalities Test; PVSAT: Paced Visual Serial Addition Test (4 second and 2 second versions); CRT: Choice Reaction Time Test; CRT-SRT: Choice Reaction Time minus Simple Reaction Time; STROOP: Stroop Colour-Word Test; SRT: Simple Reaction Time Test

Table 6a. Sensitivity and specificity table for the computerized battery when compared to the MACFIMS

<table>
<thead>
<tr>
<th>Threshold - Impaired on at least:</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/7</td>
<td>83.3</td>
<td>68.4</td>
</tr>
<tr>
<td>2/7</td>
<td>64.3</td>
<td>87.7</td>
</tr>
<tr>
<td>3/7</td>
<td>52.4</td>
<td>94.7</td>
</tr>
<tr>
<td>4/7</td>
<td>38.1</td>
<td>96.5</td>
</tr>
<tr>
<td>5/7</td>
<td>21.4</td>
<td>98.2</td>
</tr>
<tr>
<td>6/7</td>
<td>7.1</td>
<td>98.2</td>
</tr>
<tr>
<td>7/7</td>
<td>0</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Table 6b. Sensitivity and specificity tables for selective combinations of computerized tests

<table>
<thead>
<tr>
<th>Test(s)</th>
<th>Impairment Threshold</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-SDMT</td>
<td>1/1</td>
<td>66.7</td>
<td>87.7</td>
</tr>
<tr>
<td>C-SDMT, PVSAT-4</td>
<td>1/2</td>
<td>81.0</td>
<td>87.7</td>
</tr>
<tr>
<td>C-SDMT, PVSAT-4, PVSAT-2</td>
<td>1/3</td>
<td>83.3</td>
<td>87.7</td>
</tr>
<tr>
<td>C-SDMT, PVSAT-4, CRT</td>
<td>1/3</td>
<td>78.4</td>
<td>80.4</td>
</tr>
<tr>
<td>C-SDMT, PVSAT-4, CRT-SRT</td>
<td>1/3</td>
<td>83.8</td>
<td>78.2</td>
</tr>
<tr>
<td>C-SDMT, PVSAT-4, PVSAT-2, CRT, CRT-SRT</td>
<td>1/5</td>
<td>86.5</td>
<td>74.5</td>
</tr>
</tbody>
</table>

C-SDMT: Computerized Symbol Digit Modalities Test; PVSAT: Paced Visual Serial Addition Test (4 second and 2 second versions) CRT: Choice Reaction Time Test; CRT-SRT: Choice Reaction Time minus Simple Reaction Time

and a specificity of 87.7% in relation to the MACFIMS.

Table 7 shows the calculations for sensitivity and specificity using the threshold of at least one impaired test out of three. The positive predictive value (PPV) was 83.3% signifying that if a patient received a positive test result, there was an 83.3% chance that impairment was present. The negative predictive value (NPV) was 87.7% indicating that a patient receiving a negative result would not have cognitive impairment 87.7% of the time. A ROC analysis revealed an area under the curve (AUC) of 0.869, p < 0.001 (Figure 6).

Sensitivity and specificity were calculated for each disease type to ascertain that the computerized battery can be used with SPMS and PPMS patients as well as those with RRMS. These data can be seen in Table 8.
Table 7. Sensitivity and specificity table for the computerized screen (C-SDMT, PVSAT-4, PVSAT-2) compared to MACFIMS impairment for MS patients (N = 99)

<table>
<thead>
<tr>
<th></th>
<th>MACFIMS cognitive impairment</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Impaired</td>
<td>Not impaired</td>
</tr>
<tr>
<td>Computerized screen impairment</td>
<td>Impaired</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Not impaired</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td>57</td>
</tr>
</tbody>
</table>

Sensitivity = $\frac{\# \text{ of true positives}}{(\# \text{ of true positives} + \# \text{ of false negatives})}$

$\frac{35}{42} \times 100 = 83.3\%$

Specificity = $\frac{\# \text{ of true negatives}}{(\# \text{ of true negatives} + \# \text{ of false positives})}$

$\frac{50}{57} \times 100 = 87.7\%$

Percent Correctly Classified = $\frac{(35 + 50)}{99} \times 100 = 85.9\%$
Figure 6. ROC Curve: The computer generated screening battery relative to the MACFIMS

Receiver operating characteristic (ROC) curve of the computerized screening battery (the computerized battery referred to contains the Computerized Symbol Digit Modalities Test, Paced Visual Serial Addition Test 4 second, Paced Serial Visual Addition Test 2 second) compared to MACFIMS global impairment. AUC: Area under the curve

Table 8. Sensitivity and specificity of the computerized screen (C-SDMT, PVSAT-4, PVSAT-2) compared to MACFIMS impairment for RRMS, SPMS, and PPMS patients

<table>
<thead>
<tr>
<th>Disease Course</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRMS</td>
<td>86.7%</td>
<td>79.3%</td>
</tr>
<tr>
<td>SPMS</td>
<td>80.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td>PPMS</td>
<td>85.7%</td>
<td>90.0%</td>
</tr>
</tbody>
</table>

RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis
e. Correlations between computerized and non-computerized tests

The strength of the association between the computerized tests used in the final screening battery and their conventional analogues was explored using Pearson correlations. The number of correct responses on the PVSAT-4 was significantly correlated with that of the PASAT-3 (r = 0.71, p < 0.001). Similarly, PVSAT-2 was significantly correlated with PASAT-2 (r = 0.76, p < 0.001). The raw scores of the C-SDMT correlated inversely with the number of correct responses on the conventional SDMT (r = -0.82, p < 0.001).

f. Predictors of cognitive impairment

To explore the influences of a number of factors on cognitive dysfunction as defined by impairment on the computerized battery (i.e., failure of at least one of three tests), a logistic regression analysis was undertaken with the following potential predictor variables: age, gender, EDSS, education, illness duration, HAD depression, HAD anxiety, and ANART. The results, displayed in Table 9, show that only the ANART emerged as a significant predictor of cognitive impairment.

Table 9. Logistic regression analysis of computerized screen impairment

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>Wald</th>
<th>p</th>
<th>Exp(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.02</td>
<td>0.59</td>
<td>0.444</td>
<td>1.02</td>
</tr>
<tr>
<td>Gender</td>
<td>-0.87</td>
<td>2.34</td>
<td>0.126</td>
<td>0.42</td>
</tr>
<tr>
<td>Education</td>
<td>-0.01</td>
<td>0.00</td>
<td>0.963</td>
<td>1.00</td>
</tr>
<tr>
<td>EDSS</td>
<td>0.15</td>
<td>2.01</td>
<td>0.156</td>
<td>1.16</td>
</tr>
<tr>
<td>Illness Duration</td>
<td>-0.04</td>
<td>1.22</td>
<td>0.269</td>
<td>0.96</td>
</tr>
<tr>
<td>Depression</td>
<td>0.07</td>
<td>1.02</td>
<td>0.313</td>
<td>1.08</td>
</tr>
<tr>
<td>Anxiety</td>
<td>-0.03</td>
<td>0.22</td>
<td>0.637</td>
<td>0.97</td>
</tr>
<tr>
<td>ANART</td>
<td>-0.09</td>
<td>5.42</td>
<td>0.007</td>
<td>0.91</td>
</tr>
</tbody>
</table>

EDSS: Expanded Disability Status Scale; ANART: American National Adult Reading Test
g. Test-retest reliability

A subset of patients (N = 30) and healthy controls (N = 19) completed a retest approximately 71.7 (SD = 26.2) days after initial testing. Test-retest analyses revealed significant intra-class correlation coefficients for every computerized test. These data are shown in Table 10.

Table 10. Test-retest reliability for computerized tests using intra-class correlation

<table>
<thead>
<tr>
<th>Test</th>
<th>Intra-class correlation coefficient</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-SDMT</td>
<td>0.927</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>PVSAT-4</td>
<td>0.483</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>PVSAT-2</td>
<td>0.747</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>CRT</td>
<td>0.849</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>SRT</td>
<td>0.945</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>STROOP</td>
<td>0.814</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

C-SDMT: Computerized Symbol Digit Modalities Test; PVSAT: Paced Visual Serial Addition Test (4 second and 2 second versions); CRT: Choice Reaction Time Test; SRT: Simple Reaction Time Test; STROOP: Stroop Colour-Word Test

3.2.3 Order of test administration

a. Demographic and neurological comparisons

Comparisons between patients who were administered the computer generated screen first and those who completed the MACFIMS first are presented in Table 11. Patients who were administered the MACFIMS first had significantly higher EDSS scores but were not more depressed (t = 1.0, p = 0.921) or anxious (t = 1.8, p = 0.77).
Table 11. Demographic and neurological comparisons between patients who were administered the computerized battery vs. the MACFIMS first

<table>
<thead>
<tr>
<th></th>
<th>Completed computerized screen first (N = 74)</th>
<th>Completed MACFIMS first (N = 25)</th>
<th>t-test / x²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Mean (SD)</td>
<td>47.6 (9.6)</td>
<td>51.3 (9.6)</td>
<td>t = -1.7</td>
<td>p = 0.097</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>52 (70.3%)</td>
<td>15 (60.0%)</td>
<td>x² = 0.9</td>
<td>p = 0.343</td>
</tr>
<tr>
<td>Premorbid IQ</td>
<td>113.3 (8.2)</td>
<td>111.7 (8.4)</td>
<td>t = 0.8</td>
<td>p = 0.413</td>
</tr>
<tr>
<td>Years of education</td>
<td>14.9 (2.1)</td>
<td>14.6 (2.7)</td>
<td>t = 0.5</td>
<td>p = 0.618</td>
</tr>
<tr>
<td>Illness duration (yrs)</td>
<td>11.1 (8.0)</td>
<td>12.8 (10.3)</td>
<td>t = -0.8</td>
<td>p = 0.405</td>
</tr>
<tr>
<td>EDSS</td>
<td>3.6 (2.6)</td>
<td>5.4 (2.0)</td>
<td>t = -3.4</td>
<td>p = 0.001</td>
</tr>
<tr>
<td>Disease course</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RRMS</td>
<td>42</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPMS</td>
<td>27</td>
<td>11</td>
<td>x² = 28.8</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>PPMS</td>
<td>5</td>
<td>12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EDSS: Expanded Disability Status Scale; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis

b. Cognitive comparisons

Of the patients who were administered the computerized battery first (N = 74), 29 (39.2%) were impaired on the MACFIMS, compared to 13 (52.0%) impaired in the group that was administered the MACFIMS first (N = 25). This difference in global impairment on the MACFIMS was not significant (x² = 1.256, p = 0.262). Thirty-one of 74 (41.9%) patients who were administered the computerized battery first compared to 11 of 25 (44.0%) patients in the MACFIMS first group were impaired on the computerized battery. This difference was, once again, not significant (x² = 0.034, p = 0.854).
A sensitivity and specificity analysis of the computerized battery (i.e., C-SDMT, PVSAT-4, PVSAT-2) in the group that was administered the computerized tests first revealed a sensitivity of 82.8% and a specificity of 84.4% (at a threshold of one impaired test out of three) relative to MACFIMS global impairment. In the group that was administered the MACFIMS first, the same analysis gave a sensitivity of 84.6% and a specificity of 100.0%.

A logistic regression was conducted to assess the predictive properties of the EDSS and ANART on cognitive impairment as defined by the computerized battery, initially on the group that was administered the computerized tests first and subsequently on the group that was administered the MACFIMS first. EDSS was not a significant predictor of cognitive impairment in either group. However, the ANART predicted global impairment when the computerized battery was given first (p = 0.05) but not second (p = 0.08).

3.2.4 Computerized vs. non-computerized tests: C-SDMT, PVSAT-4, PVSAT-2 vs. SDMT, PASAT-3, PASAT-2

a. SDMT, PASAT-3, PASAT-2

Sensitivity and specificity analyses were performed for the non-computerized SDMT, PASAT-3, and PASAT-2 in order to compare how the computerized tests stand up against the conventional tests. A threshold of at least one impaired test out of three gave a sensitivity of 94.9% and a specificity of 71.4%, with an overall predictive value (percent correctly classified) of 81.1%.

b. C-SDMT, PASAT-3, PASAT-2

The PVSAT-4 and PVSAT-2 were replaced with the PASAT-3 and PASAT-2 to assess whether this improved the sensitivity and specificity of the screening battery. It did not, yielding a result of 82.1% and 80.7% respectively.

c. SDMT, PVSAT-4, PVSAT-2

Finally, the computerized PVSAT-4 and PVSAT-2 were paired with the non-computerized SDMT to reveal a sensitivity of 87.2% and a specificity of 78.6%.
Chapter 4
Discussion

Developing a valid computer generated assessment that is quick and easy to administer and
requires limited motor ability to complete were the primary aims of the study. This screening
tool could be useful in a busy clinical setting where conventional testing, be it a brief or more
comprehensive neuropsychological assessment, is not a practical option.

To summarize, 99 MS patients and 98 healthy controls comparable in age, gender, years of
education, and premorbid IQ were administered a new computer generated battery of five
cognitive tests. The MS patients were also tested with seven MACFIMS tests (11 indices) for
which healthy norms already exist. As per the scoring instructions provided in the MACFIMS
manual, patients who failed at least two out of 11 indices were deemed globally impaired on the
MACFIMS (i.e., 42.4% of the patient sample). After comparing global impairment on the
computerized battery with that of the MACFIMS, the computerized screening instrument was
condensed to three tests (i.e., the C-SDMT, the PVSAT-4, and the PVSAT-2) to improve
sensitivity and specificity measures. Failure on at least one test out of the three (i.e., a score
below -1.5 SD of the healthy control mean) on the computer generated battery also yielded an
impairment rate of 42.4%.

The three computer generated tests administered with technician supervision revealed good
sensitivity and specificity (i.e., 83.3% and 87.7%, respectively) in determining the presence of
cognitive dysfunction when compared to impairment on the MACFIMS. Each test successfully
distinguished between patients and healthy controls as well as between cognitively impaired and
intact patients. This establishes good criterion validity. Construct validity is underscored by the
highly significant correlations between the computerized tests and their paper and pencil
counterparts. All the computer generated tests demonstrated high test-retest reliability. Adding to
the utility of the computer generated screening instrument is the fact that the results appear
unaffected by moderate levels of anxiety and depression. Only premorbid IQ (i.e., as measured
by the ANART) emerged as a significant predictor of global impairment, a finding in keeping
with current research relating to cognitive reserve (Sumowski et al., 2009). In a study of 58
patients and 43 healthy subjects only the patients with lower levels of cognitive reserve,
measured with a reading test, showed cognitive deficits when compared to controls on tasks of complex information processing and verbal learning and memory (Sumowski et al., 2009).

In order to determine whether the order of test administration had an effect on cognitive outcome, one quarter of all patients were administered the MACFIMS prior to the computerized battery and the rest completed the computer tests first. Demographic comparisons revealed that the former had higher EDSS scores. A logistic regression, however, demonstrated that the EDSS did not contribute to global cognitive impairment on the computerized screen whether administered first or second.

The findings from this study add to a small literature devoted to developing computerized cognitive batteries for use in MS patients (Wilken et al., 2003; Achiron et al., 2007; De Sonneville et al., 2002; Lazeron et al., 2006; Younes et al., 2007; Edgar et al., 2011). Here, however, we tried to improve on the methodologies of preceding studies in several important ways. Table 12 summarizes how the present study differs from its predecessors.

To begin with, the sample studied is much larger than that of previous studies and is representative of the broader MS population, not only in terms of age and gender but also with respect to the three main disease types that comprise clinically confirmed multiple sclerosis. The proportion of patients with relapsing-remitting (44.4%), secondary progressive (38.4%) and primary progressive (17.2%) disease is comparable to community prevalence rates (Noseworthy et al., 2000; Miller & Leary, 2007; Tremlett et al., 2006). Many earlier studies validated computerized measures in relapsing-remitting patients only in order to exclude those more disabled who could not complete the testing (Wilken et al., 2003; Achiron et al., 2007; Edgar et al., 2011). This selection bias arose because certain computerized tests have a prominent motor component which, in effect, places them outside the functional limits of patients with limited motor dexterity. This challenge was met by selecting tests accordingly to ensure that exclusion based on motor ability would seldom be necessary. The three tests that were chosen for the final screening tool have only a limited motor component, namely verbal responses. The higher EDSS score in the present sample demonstrates that motor deficits did not exclude the majority of patients from completing the computer generated tests. A further analysis of sensitivity and specificity of the computerized screen (C-SDMT, PVSAT-4, PVSAT-2) compared to the
Table 12. Comparison of characteristics and results between previous computerized battery MS studies and the current study

<table>
<thead>
<tr>
<th></th>
<th>Wilken et al., 2003</th>
<th>Achiron et al., 2007</th>
<th>De Sonneville et al., 2002</th>
<th>Younes et al., 2007</th>
<th>Edgar et al., 2011</th>
<th>Current Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample Size</strong></td>
<td>50</td>
<td>58</td>
<td>53</td>
<td>40</td>
<td>43</td>
<td>99</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>43.0 (10.9)</td>
<td>41.5 (10.0)</td>
<td>48.2 (12.6)</td>
<td>45.0 (10.2)</td>
<td>38.8 (10.5)</td>
<td>48.5 (9.7)</td>
</tr>
<tr>
<td><strong>Education (Years)</strong></td>
<td>15.3 (2.1)</td>
<td>15.4 (2.8)</td>
<td>15.0 (2.1)</td>
<td>14.8 (2.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gender (% Female)</strong></td>
<td>70%</td>
<td>71%</td>
<td>65%</td>
<td>70%</td>
<td>68%</td>
<td></td>
</tr>
<tr>
<td><strong>Disease Course</strong></td>
<td>100% RR</td>
<td>76% RR, 7% SP, 17% probable MS</td>
<td>30% RR, 34% SP, 36% PP</td>
<td>66% RR, 12.5% SP, 12.5% PP, 9% RP</td>
<td>100% RR</td>
<td>45% RR, 38% SP, 17% PP</td>
</tr>
<tr>
<td><strong>EDSS</strong></td>
<td>2.2 (1.0)</td>
<td>2.6 (1.8)</td>
<td>4.7 (2.0)</td>
<td>2.8 (1.2)</td>
<td>4.1 (2.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Gold Standard</strong></td>
<td>Detailed cognitive evaluation</td>
<td>NPSBMS</td>
<td>Detailed cognitive evaluation</td>
<td>DSST, PASAT</td>
<td>MACFIMS</td>
<td></td>
</tr>
<tr>
<td><strong>Battery</strong></td>
<td>ANAM</td>
<td>MCCB</td>
<td>ANT</td>
<td>CSI</td>
<td>CDR</td>
<td>New</td>
</tr>
<tr>
<td><strong>Administration Time (Min)</strong></td>
<td>30</td>
<td>50</td>
<td>90</td>
<td>30</td>
<td>15-20</td>
<td>10</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>97.5%</td>
<td></td>
<td>83.3%</td>
<td>83.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>87.5%</td>
<td></td>
<td>85.7%</td>
<td>87.7%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RR: relapsing-remitting; SP: secondary progressive; PP: primary progressive; NPSBMS: Neuropsychological Screening Battery for Multiple Sclerosis; DSST: Digit Symbol Substitution Test; PASAT: Paced Auditory Serial Addition Test; MACFIMS: Minimal Assessment of Cognitive Function in Multiple Sclerosis; ANAM: Automated Neuropsychology Assessment Metrics; MCCB: Mindstreams Computerized Cognitive Battery; ANT: Amsterdam Neuropsychological Tasks; CSI: Cognitive Stability Index; CDR: Cognitive Drug Research battery
MACFIMS according to disease course revealed that the battery can be used successfully with RRMS, SPMS, and PPMS patients as it retains high enough sensitivity and specificity for each group. Finally, the present protocol had the benefit of the MACFIMS as the “gold standard” determinant of cognitive dysfunction, unlike previous studies where the computerized tests were compared either to brief screening batteries, or a collection of neuropsychological measures not necessarily considered optimum for teasing out cognitive problems in MS patients.

The MACFIMS, a comprehensive neuropsychological assessment assembled specifically to detect cognitive dysfunction in MS patients, was used to validate the computerized battery. The MACFIMS comprises seven tests which assess five main cognitive domains often impaired in MS patients. The prevalence of cognitive impairment in MS is difficult to determine as it depends on the definition of cognitive impairment as well as which population of MS patients (i.e., RRMS, SPMS, etc., terms confounded by age) is being studied. The prevalence of impairment in our study was 42.4%, which replicates previous findings in community samples. In a study of 100 MS patients and 100 healthy controls matched to patients on age, education, and gender, participants were administered a neuropsychological battery consisting of 31 indices and impairment was defined as four or more impaired indices (Rao et al., 1991a). Forty-eight MS patients and five healthy controls were impaired on the battery. An overall rate of impairment for the MS group was 43% after subtracting the 5% false positive rate. In a separate study 147 community based patients and 34 gender and education matched patients with rheumatoid arthritis were tested with a cognitive battery containing the Rivermead Behavioural Memory Test (RBMT), the Modified Wisconsin Card Sorting Test (MWCST), the COWAT, and two tests of general intellectual functioning (i.e., the verbal subscales of the Wechsler Adult Intelligence Scale - Revised (WAIS-R) and Raven’s Standard Progressive Matrices) (McIntosh-Michaelis et al., 1991). Patients were considered impaired if they failed at least one of the RBMT, MWCST, or COWAT and had deficits on both general intellectual measures. The global impairment rate for the MS group was 46% and 12% in the rheumatoid arthritis group. More recently, Duquin and colleagues (2008) showed that the rate of cognitive impairment varies according to sample selection. In a subgroup of their subjects (n=57) whose composition is analogous to the 99 MS patients reported on in this thesis, cognitive impairment was found in 45.6% of subjects.

The computer generated screen performed well in relation to the MACFIMS in part because the three measures (i.e., the C-SDMT, PVSAT-4, and PVSAT-2) are similar to the original paper
and auditory versions. Scoring the computerized tests differs however: in the C-SDMT, the mean time to match nine symbols with numbers over eight trials is used, unlike the SDMT where the number of correct answers in 90 seconds is recorded. Although the SDMT and the C-SDMT both have the highest rate of impairment within their respective batteries, 10% more patients failed the paper version of the test. Several possible reasons could account for this discrepancy. First of all, as previously mentioned, the scoring procedure differs in each test. Allowing patients sufficient time to complete all trials could potentially aid patients who start the test slowly and speed up toward the end. Second, because the symbols are presented nine at a time in a single line (see Figure 2), patients do not have to move their eyes and head as much as they would in the paper version. This reduces the motor component involved in testing which possibly amplifies the rate of impairment seen in the conventional SDMT. Of note, however, is that this finding is at odds with a previous report in which the same computerized version of the SDMT outperformed the paper version (37% versus 29% of patients were impaired). That said, the overall percentage of patients who were deemed impaired on the C-SDMT in Akbar et al.’s (2011b) study was 37%, which is almost identical to the 35.4% figure reported in the present study indicating that the computerized test has high reliability.

The finding that the SDMT had the highest rate of impairment compared to all other tests, with more than a third of patients failing this task, both in the computerized screen (i.e., C-SDMT) and in the MACFIMS, supports recent research in which the SDMT was shown to be the most sensitive of all cognitive tasks (Benedict et al., 2006). The SDMT has also consistently been shown to correlate with markers of brain pathology more robustly than any other cognitive measure. A study examining neuroimaging indices and cognitive impairment as measured by a modified BRB-N in 37 patients demonstrated that the SDMT was the cognitive measure most strongly associated with both central (ventricular) atrophy and lesion volume (Christodoulou et al., 2003). In a study of 37 patients and 27 matched healthy controls undergoing MRI and neuropsychological testing with the MACFIMS battery, linear regression analyses showed that, of all 11 cognitive indices, the SDMT had the highest correlation with third ventricle width, which was the most significant predictor of global cognitive impairment (Benedict et al., 2004b). The SDMT also had the highest correlation with brain parenchymal fraction, which also predicted overall cognitive impairment. In a more recent study, Benedict and colleagues (2009) examined mesial temporal lobe (MTL) (hippocampus, amygdala) and deep grey matter (DGM)
MRI indices in 50 patients who also underwent cognitive testing. Of all neuropsychological tests administered the SDMT was the most sensitive, correlating robustly with both DGM and MTL atrophy, especially the thalamus (Pearson r = 0.62, p < 0.001).

Given the ease of administration, high sensitivity and “subject friendly” aspect to testing, the SDMT has emerged as the cognitive test of choice in screening for cognitive dysfunction in MS patients. For years this position was held by the PASAT which still remains the single cognitive measure in the Multiple Sclerosis Functional Composite (Fischer et al., 1999). The PASAT, however, has been criticized as too difficult and anxiety provoking for some MS patients (Benedict et al., 2002). In a study of 400 MS patient and 100 healthy controls, Drake and colleagues examined the validity of the original MSFC (i.e., with the PASAT), and the MSFC in which the PASAT was replaced with the SDMT. Both tests had similar test-retest reliability but in a logistic regression analysis of the cross-sectional portion of the study the SDMT had slightly better validity (AUC = 92% vs. 90%) in predicting MS diagnosis, disease course, and work disability (Drake et al., 2010). The present study, while confirming the utility of the PASAT, goes beyond this and shows that a visual version, which is slightly slower (four versus three second intervals) in the first trial and potentially easier to perform than the original auditory version, emerged as a more useful screening index when combined with the C-SDMT.

When it comes to the administration of cognitive tests, there is a widening array of approaches. The most frequent method involves patients being tested by neuropsychologists or trained psychometricians working for a neuropsychologist. By introducing computer based tests into the process, this reliance on neuropsychological expertise has been loosed. At one end of this evolving spectrum are fully automated tests that potentially would require no supervision by an administrator. To date, there are no published reports of such an approach involving MS patients. Rather, all computerized batteries used with MS patients require the presence of a tester to oversee the process (Wilken et al., 2003; Achiron et al., 2007; De Sonneville et al., 2002; Lazeron et al., 2006; Younes et al., 2007; Edgar et al., 2011). The new computer generated battery falls into this category. The methodology that has been developed does not require a tester with a particular psychological expertise. All that is needed is for a person to read a script containing the instructions, to push a key to begin and end a test, and in the case of the PVSAT, to record the errors. While having a fully automated, non administrator dependent battery available for use with MS subjects would be preferable from a logistics perspective, the obvious
challenge is to avoid the potentially negating effects of having a cognitively impaired patient in the ‘driver seat’ compromise the testing process.

Cognitive dysfunction in MS patients casts a wide shadow potentially impairing multiple aspects of a patient’s life. In Rao et al.’s (1991b) seminal study MS patients with and without cognitive decline were compared. The former were less likely to be working and were more dependent on others in terms of daily living activities. Impaired patients also had difficulties with personal hygiene and following recipes. Patients in the impaired group were rated as more socially dysfunctional too given their tendency to withdraw from relationships, avoid interpersonal contacts and display confusion in a social setting. Importantly, these difficulties were thought to arise independently of depression. In a more recent study, Benedict and colleagues (2005) replicated those findings by linking cognitive impairment with vocational status. A logistic regression analysis revealed that the personality trait of conscientiousness as reported by an informant, disease duration, and cognitive deficits on three tests: SDMT, WCST perseverations, and JLO predicted employment status.

These real life findings take on even greater salience in two clinical situations that have, until recently, not received much attention. The first is benign MS, generally defined as little or no neurological disability for at least 15 years after clinical onset of the disease. Amato and colleagues (2006) conducted a wide ranging behavioural study in 163 MS patients classified as having a benign course (i.e., an EDSS score of ≤ 3.0 at least 15 years after diagnosis). All subjects were given the BRB-N (i.e., SRT, 10/36 Spatial Recall Test, PASAT, SDMT, and WLG) and the Stroop test, and depression was assessed using the Montgomery and Asberg Depression Rating Scale (MADRS). Patients were deemed impaired if they scored below the fifth percentile of a group of 111 demographically matched healthy controls. Global impairment was defined as failure on three or more of the six cognitive tests. The results revealed that 74 (45%) patients were cognitively impaired. This result calls into question the validity of the ‘benign’ label as does a recent longitudinal report. In a large, 30 year observational study 874 patients were examined with respect to their Disability Status Scale (DSS) scores and patients who were labeled as having clinically definite benign multiple sclerosis (CDBMS) were split into two groups (Leray et al., 2013). Patients who had a DSS score ≤ 2.0 at 10 years were labeled as CDBMS1 (N = 252) while those with a DSS score ≤ 3.0 were placed into a group designated CDBMS2 (N = 301). Twenty years after diagnosis, only 41.7% of patients in the CDBMS1
group and 53.8% of the CDBMS2 group maintained a DSS score ≤ 2.0 and ≤ 3.0, respectively. Of the 56 CDBMS1 patients followed for a third decade only 41.1% retained a DSS score ≤ 2.0. Similarly, only 59.5% of the 74 CDBMS2 patients followed up remained at a DSS score ≤ 3.0 at 30 years after onset of disease. This study demonstrates that a benign course in the first 10 years of illness does not necessarily predict a favourable outcome in the subsequent decades of disease and a new definition of benign MS may be warranted.

The second condition that has recently been investigated is that of radiologically isolated syndrome (RIS) which refers to lesions suggestive of MS found unexpectedly in subjects undergoing MRI testing. An in depth neuropsychological study suggests these hitherto lesions considered ‘silent’ are not so clinically quiet after all. In a study of 26 RIS patients, 26 MS patients, and 26 healthy controls cognitive performance was assessed using a French adaptation of the BRB-N and three additional tests (Lebrun et al., 2010). The RIS and MS groups performed significantly worse than healthy controls on the PASAT, verbal fluency, the code of the WAIS-R (similar to the SDMT), a digit span test, a cross-tapping test measuring resistance to interference, and a Go-No-Go test which measures inhibition. When compared to the MS patients, the RIS group performed significantly better only on the digit span and cross-tapping test.

4.1 Limitations

The present study is not without certain limitations. Although the semi-automated computerized tests require limited motor involvement, the oral component of testing may present a problem for patients with dysarthria. This point is however, equally relevant in the conventional SDMT and PASAT tests. In addition, while the PVSAT does have a working memory component (Litvan et al., 1988), it is thought to be primarily a test of information processing speed and attention. As such, the present battery lacks a substantial memory component, thereby weakening the scope of the cognitive inquiry. In deciding which tests to include or exclude for this battery, compromises were necessary. Concerns over administration time in the context of delayed recall therefore led to the omission of a specific test of working memory. Finally, there is a possibility of tester bias because one tester administered both the computerized screening battery and the MACFIMS. If present, however, it was moderated by the fact that scores from the computer generated battery were not accessible to the tester until the full test session was over, PVSAT apart. Even here what constituted a pass or fail was not known at the time of testing.
4.2 Future Directions

Five main areas of future research have been defined.

4.2.1 Larger normative sample

The main focus of future research for this specific screening instrument is the collection of a larger normative sample. This would allow for a greater database of normative scores that can then be used to create an automated scoring system within the test program. Efforts are underway in this regard. In addition, to facilitate the use of these tests, algorithms need to be programmed based on the normative data that will allow the computer to automatically score the data on test completion. In this way the tester can immediately be informed as to a patient’s cognitive status. This development, made possible by the use of computers, removes the delay, often lengthy, associated with the scoring of conventional neuropsychological tests.

4.2.2 Parallel versions

At present, serial versions of the computerized battery do not exist. Thus, the battery cannot be used for longitudinal research because of the potential confounder of practise effects. We now know that MS patients, notwithstanding the presence of cognitive dysfunction, can still benefit substantially from practise. This has been revealed in a study of 90 CIS patients whose cognition was monitored annually for up to five years (Glanz et al., 2012). Practice effects were noted on the SDMT, PASAT-3, PASAT-2, and COWAT. Practice effects for the SDMT appeared to diminish after the first year making it a useful tool in longitudinal research, unlike scores on the PASAT and COWAT which continued to improve over the course of the five years. In order to limit the effects of practise, currently available batteries contain parallel versions. For example, there are 15 versions of the BRB-N and at least two versions of each of the MACFIMS tests. The presence of the versions opens up these batteries to use in treatment studies, something that at present eludes the computerized battery presented here. It is with this in mind that serial versions of the current computerized battery should be developed and validated.

4.2.3 Working memory test

The absence of a working memory test should be corrected, at the expense of jettisoning the Stroop. The expert panel of neuropsychologists involved in formulating the MACFIMS identified working memory as the main cognitive deficit associated with MS along with delayed
information processing speed (Benedict et al., 2002). Given the failure of the Stroop to emerge as a powerful predictor of cognitive dysfunction in the present study, replacing it with a memory test offers that opportunity to boost the battery’s sensitivity and specificity.

4.2.4 MRI correlates

Determining the strength of the association between the computerized indices and MRI metrics could further boost construct validity of the test. Performance on the SDMT and PASAT have been associated with different MRI metrics of brain pathology including global atrophy (Benedict et al., 2004b), regional atrophy, most notably of the thalamus (Benedict et al., 2004b; Houtchens et al., 2007) total lesion volume (Lazeron et al., 2005; Sperling et al., 2001) and indices of normal appearing brain tissue as demonstrated by Diffusion Tensor Imaging (Rovaris et al. 2002).

4.2.5 Guidelines for clinicians

Finally, a template needs to be developed to assist clinicians not necessarily familiar with cognitive testing when it comes to interpreting the results, providing guidelines on how best to break the news of impairment to patients and suggesting strategies that can offset some of the limitations associated with these impairments. While treating cognitive impairment is a challenge, there are certain interventions that offer benefits, ranging from easier to implement compensatory techniques (Shevil and Finalyson, 2010) to more complex, labour intensive remedial approaches that require a specialized expertise (Goverover et al., 2008; Goverover et al., 2011).

4.3 Conclusions

In conclusion, the semi-automated computerized screen (i.e., C-SDMT, PVSAT-4, and PVSAT-2) is a valid and reliable measure of cognitive dysfunction. The advantages inherent in this battery (i.e., short administration time, minimal expertise on the part of the tester, and absence of a significant motor component) make it a useful tool for routine examination in a busy clinical setting.

In completing this study, the goal was to create and validate a tool which could be widely used due to its simplicity and efficiency. This research is an addition to a small but growing number of
studies that support the benefits of standardized, computerized cognitive testing for patients with MS. Although a useful tool that boasts a high sensitivity and specificity for detecting cognitive impairment, it should be noted that the computerized screen is not meant to replace comprehensive neuropsychological testing but rather to address the lack of practical resources that are needed for screening large numbers of patients. It should be regarded as a first step that ultimately leads to treatment.

It is also important to note that while these tests are easy to administer and can be automatically scored by a computer, great care must be taken in determining what the results mean and how this information is conveyed to patients.
References


Copyright Acknowledgements

Aspects of this thesis have appeared in two publications to date:
