Using Computers to Assess Cognition in MS: Improving Tried and Tested Indices to Capture Real World Challenges

By

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ABSTRACT

Cognitive dysfunction is common in people with multiple sclerosis (MS) and causes limitation in activities of daily living. Current cognitive screens are limited by time and cost requirements and they lack ecological validity. The objective of the present study was to develop an improved method of cognitive assessment using real-world distracters. A sample of 102 MS subjects and 69 healthy controls underwent testing with a modified computerized Symbol Digit Modalities Test (c-SDMT) and the Minimal Assessment of Cognitive Functioning in MS battery. Half completed the distracter c-SDMT and half non-distracter. Relative to the traditional SDMT, significantly more MS subjects were impaired on the distracter c-SDMT, but not on the non-distracter test. The distracter test had a sensitivity of 82% and specificity of 80% in detecting global cognitive impairment. The incorporation of distracters improves the sensitivity of the c-SDMT and offers a quick and easy method for detecting cognitive dysfunction.

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CONTRIBUTIONS

Anthony Feinstein – Principle investigator and supervisor on the project; assisted in designing and conducting the study, statistical analysis and editing of the thesis

Lisa Walker – Co-investigator on the project; assisted in study design and subject recruitment

Nathan Herrmann – Program Advisory Committee member; guided the project to completion, assisted in statistical analysis and editing of the thesis

Richard Swartz – Program Advisory Committee member; guided the project to completion, assisted in statistical analysis and editing of the thesis

Alex Kiss – Assisted with statistical analysis

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

7/24: 7/24 Spatial Recall Test

10/36: 10/36 Spatial Recall Test

ACC: Anterior Cingulate Cortex

APOE: Apolipoprotein E

BDNF: Brain Derived Neurotrophic Factor

BICAMS: Brief International Cognitive Assessment for Multiple Sclerosis

BRB-N: Brief Repeatable Battery of Neuropsychological Tests

BVMT-R: Brief Visuospatial Memory Test – Revised

CIS: Clinically Isolated Syndrome

CNS: Central Nervous System

COWAT: Controlled Oral Word Association Test

c-SDMT: Computerized Symbol Digit Modalities Test

CSF: Cerebrospinal Fluid

CVLT-II: California Verbal Learning Test – Second Edition

D-KEFS: Delis Kaplan Executive Function System

DLPFC: Dorsolateral Prefrontal Cortex

DTI: Diffusion Tensor Imaging

EDSS: Expanded Disability Status Scale

HADS: Hospital Anxiety and Depression Scale

HC: Healthy Control

ICC: Intraclass Correlation Coefficient

JLO: Judgement of Line Orientation

LAS: Leisure Activity Scale

MACFIMS: Minimal Assessment of Cognitive Functioning In Multiple Sclerosis

M-FIS: Modified Fatigue Impact Scale

MS: Multiple Sclerosis

MSFC: Multiple Sclerosis Functional Composite

MRI: Magnetic Resonance Imaging

MTI: Magnetization Transfer Imaging

NPV: Negative Predictive Value

PASAT: Paced Auditory Serial Addition Test

PPMS: Primary Progressive Multiple Sclerosis

PPV: Positive Predictive Value

RIS: Radiologically Isolated Syndrome

ROC: Receiver Operating Characteristic

RRMS: Relapsing Remitting Multiple Sclerosis

SDMT: Symbol Digit Modalities Test

SPMS: Secondary Progressive Multiple Sclerosis

SRT: Selective Reminding Test

WAIS-III: Wechsler Adult Intelligence Scale – Third Edition

WCST: Wisconsin Card Sorting Test

WMC: Working Memory Capacity

WTAR: Wechsler Test of Adult Reading

CHAPTER 1: INTRODUCTION

1.1   Multiple Sclerosis

Multiple sclerosis (MS) is a chronic, autoimmune disease characterized by demyelination and degeneration of the central nervous system. Although the first pathological descriptions were made by Sir Robert Carswell and clinical accounts by Jean Cruveilhier (Murray, 2009), it was the French neurologist Jean-Martin Charcot, who first distinctively described the disease in 1868, calling it *la sclerose en plaques* (Kumar, Aslinia, Yale, & Mazza, 2011). Charcot combined historical accounts, his own clinical observations and pathological changes seen on post-mortem to better understand and characterize MS as a distinct neurological disorder.

1.1.1   Epidemiology

MS is now the leading cause of neurological disability amongst young and middle-aged adults. The incidence of MS is the highest in middle-aged adults (20 – 40 years of age), but remains relatively low in children and adults above the age of 50 (Orton et al., 2006). The global median prevalence and incidence rate of MS is estimated at 30 and 2.5 per 100 000 people, respectively (World Health Organization). When describing the geographical distribution of prevalence, countries are categorized into regions of high ($\geq$ 30 cases per 100 000), medium (5 – 29 cases per 100 000) and low (less than 5 cases per 100 000) prevalence zones. Early epidemiological studies suggested that MS was more prevalent in regions distant from the equator, however, recent studies have shown this trend to be decreasing (Alonso & Hernan, 2008).

Canada has one of the highest rates of MS worldwide at 240 cases per 100 000 people (Beck, Metz, Svenson, & Patten, 2005; J. F. Kurtzke, 2000) and approximately 1000 new cases are diagnosed each year (Poppe, Wolfson, & Zhu, 2008). Within Canada there is a large geographical variation in prevalence rates, with Quebec having the lowest rate at 180 per 100 000 and the Atlantic and Prairie regions having the highest at 340-350 per 100 000 (Beck et al., 2005).

Women are three times more likely to be affected with MS than men. Over the past few decades, there has been a trend towards an increasing sex ratio due to a selectively higher rise in the incidence of MS in women (Alonso & Hernan, 2008; Orton et al., 2006). This pattern has been reported in several countries and in Canada the female to male sex ratio now exceeds 3:1 (Orton et al., 2006). This rapid change has been attributed to be a result of environmental factors such as smoking, dietary habits, and level of physical activity.

1.1.2   Pathophysiology

MS is an inflammatory, autoimmune disease characterized by axonal demyelination, and neuronal and oligodendrocyte loss. Areas of demyelination are commonly referred to as 'plaques' and they result in impaired nerve transmission. This in turn leads to neurological symptoms. Early disease pathology involves the formation of new and active plaques in areas of the central nervous system (CNS) including the spinal cord, periventricular white matter, deep white matter, juxtacortical white matter, corpus callosum and cerebral peduncles (Kamm, Uitdehaag, & Polman, 2014). Active plaques are thought to be a result of a disrupted blood-brain barrier, which leads to the extravasation of inflammatory cells such as T-cells and macrophages (Palmer, 2013). Within the CNS, inflammatory cell activity causes structural injury

2

to myelin, making axons susceptible to damage from cytokines and chemokines. In addition to white matter damage, cortical grey matter is also affected with the presence of demyelinating lesions and atrophy (Filippi & Rocca, 2010; Lucchinetti et al., 2011).

In response to axonal injury, a remyelination process may be initiated through the recruitment of oligodendrocyte progenitor cells. This causes the formation of "shadow plaques" which are remyelinated axons with thin sheaths of myelin (Lassmann, Brück, & Lucchinetti, 2007). The extent of axon remyelination varies between individuals and is dependent on several factors such as lesion location, availability of axons within plaques and disease course (Lassmann et al., 2007; Patrikios et al., 2006). Remyelination becomes less frequent as the disease progresses.

In progressive phases of the disease, the formation of new active plaques is rare and the disease is primarily characterized by slow, diffuse atrophy of gray and white matter, and changes in the normal appearing brain tissue. With advances in imaging techniques, markers such as brain volume or atrophy are shown to be just as important as lesion volume in predicting clinical outcomes such as physical disability (Sanfilipo, Benedict, Sharma, Weinstock-Guttmann, & Bakshi, 2005). Magnetization transfer imaging (MTI) and diffusion tensor imaging (DTI) have also highlighted the important role of normal appearing white and gray matter in MS pathology.

1.1.3 Etiology

The etiology of MS is largely unknown, but epidemiological studies indicate a role of both environmental and genetic factors.

Several environmental factors are suggested to play a role in the etiology of MS. Past studies have reported a strong correlation between higher latitude and increased incidence of MS, but this correlation has decreased in the past few years as recent evidence points to the level of sunlight exposure being the putative factor (Alonso & Hernan, 2008). Indeed a higher prevalence of MS has been found in areas of low sunlight exposure (Beretich & Beretich, 2009; Ramagopalan et al., 2011; Sloka, Pryse-Phillips, & Stefanelli, 2008). With sunlight exposure, vitamin D is postulated as the protective agent and studies have shown a lower risk of MS associated with increasing serum vitamin D levels (Munger, Levin, Hollis, Howard, & Ascherio, 2006; Salzer et al., 2012). In addition, low levels of vitamin D have also been associated with increasing disability and higher risk of relapse (Runia, Hop, de Rijke, Buljevac, & Hintzen, 2012; van der Mei et al., 2007). Recently, cigarette smoking has also emerged as a viable risk factor for both susceptibility and progression of MS (Wingerchuk, 2012). Several infectious microorganisms have been suggested to increase susceptibility to MS, but the Epstein-Barr virus in particular has been heavily investigated because greater than 99% of people with MS are found to be seropositive (Ascherio & Munger, 2007).

Although no single gene has been identified as sole risk factor for MS, genetics play an influential role in the etiology of MS. Twin studies provide strong evidence for a genetic etiology, where monozygotic twins are found concordant in 24-30% of cases compared to dizygotic twins concordant in 3-5% of cases (Hansen et al., 2005; Kamm et al., 2014). The prevalence of MS has also been reported to vary in people of different ethnicities living in similar environmental conditions, which further suggests a role of genetics (Williamson, Henry, Schiffer, & Wagner, 2007). Overall, the etiology of MS cannot be attributed solely to genetics or

the environment, but rather an interaction between the two. The combination of genetic susceptibility and exposure to specific environmental risk factors leads to the greatest vulnerability.

1.1.4 Clinical Disease Course

The clinical course of MS varies between individuals and is characterized by episodes of relapses and/or disease progression. At disease onset, the most frequently reported neurological symptoms include visual disturbances (optic neuritis, blurred or double vision), motor weakness (numbness in the extremities, instability in walking, spasms), and problems with bladder and bowel control (incontinence, frequency or retention; Raine, McFarland, & Hohlfeld, 2008). In addition to physical symptoms, neuropsychological problems may be prevalent as well which include cognitive impairment (Huijbregts, Kalkers, de Sonneville, de Groot, & Polman, 2006), fatigue (Benito-León et al., 2007), and unstable mood (Arnett, Higginson, & Randolph, 2001).

Before developing definitive MS, 85% of individuals experience a single neurological attack, referred to as a 'clinically isolated syndrome (CIS)', affecting the optic nerves (optic neuritis), the brain stem or the spinal cord (Miller, Chard, & Ciccarelli, 2012). Conversion to clinically definite MS occurs in between 10-85% of individuals presenting with optic neuritis CIS (Fisniku et al., 2008; Optic Neuritis Study Group, 2008), 41-61% in spinal cord CIS (Fisniku et al., 2008; Tintore et al., 2010) and 53-60% in brainstem CIS (Fisniku et al., 2008). Furthermore, the presence of cognitive impairment in CIS is a significant risk factor predicting conversion to clinically definite MS (Zipoli et al., 2010).

Approximately 60% of people are affected by relapsing-remitting MS (RRMS), which is characterized by episodes of relapses followed by partial or complete remission. Relapses are labelled as neurological attacks in the absence of fever or infection that last for more than 24 hours (Kamm et al., 2014). Partial or full recovery from relapses can take anywhere between a few days to weeks and there is no disease progression between periods of remission. Approximately 75% of individuals with RRMS eventually go on to develop secondary-progressive MS (SPMS), which is characterized by the gradual worsening of neurological symptoms (Confavreux & Vukusic, 2006). The conversion of RRMS into SPMS may occur early in the disease process or be delayed for several years. The progression of disease in SPMS occurs at a variable rate without the presence of distinct relapses or with occasional relapses and minor remissions. Approximately 15% of individuals are also affected by primary-progressive MS (PPMS), which is characterized by a progressive disease course from symptom onset and the absence of discrete relapses and remissions. In some cases of PPMS, occasional plateaus of disease progression and temporary improvement of symptoms may occur.

Aside from the three major MS subtypes, 5-64% of individuals may also have benign MS (see Ramsaransing & De Keyser, 2006 for review). The wide variability in prevalence is due to several factors such as the varying definitions used for benign MS and the type of studies conducted (epidemiological versus clinical studies). Most commonly individuals are classified as having benign MS if they have an Expanded Disability Status Scale (EDSS) < 3 after a minimum of 10 years of disease.

1.1.5 Diagnosis

The diagnosis of MS is based on the presence of central nervous system (CNS) lesions typical of MS, disseminated in space (DIS) and time (DIT). The diagnosis can be made on clinical grounds alone if individuals present with two or more neurological attacks, with objective clinical evidence of demyelination in more than one area of the CNS or clinical evidence of one lesion along with evidence of one prior attack. With the introduction of the McDonald criteria in 2001, the diagnosis was supplemented with magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) laboratory data (McDonald et al., 2001). The use of the McDonald criteria, revised in 2005 and 2010, has resulted in earlier diagnosis with higher sensitivity and specificity, allowing clinicians to implement treatment in the CIS or relapsing-remitting stages of the disease (Polman et al., 2005, 2011). MRI findings are diagnostically helpful particularly when clinical evidence is not clear. For example, in cases where individuals present with two or more neurological attacks with objective clinical evidence of only one lesion, MRI evidence of two or more lesions disseminated in space or the occurrence of a second clinical attack implicating a different CNS site must be accompanied for diagnosis (Polman et al., 2011). The diagnosis of primary-progressive MS is made using clinical, paraclinical (e.g. MRI, evoked potentials) and laboratory (e.g. CSF analysis) observations. There must be at least 1 year of disease progression along with 2 of the following: evidence of one or more lesions disseminated in space in the brain (periventricular, juxtacortical or infratentorial), two or more lesions disseminated in space in the spinal cord, and positive CSF (Polman et al., 2011).

1.1.6   Treatment and Management

Currently there is no known cure for MS, but the common treatment for alleviating symptoms due to a relapse is a course of corticosteroids (Leary, Porter, & Thompson, 2005). Several disease modifying drugs (DMDs) are also available to slow the rate of disease progression and reduce the number of neurological attacks. Currently all FDA approved drugs are used for treating RRMS and few show promise for SPMS (for review see Kamm et al., 2014). In the absence of disease modifying treatments for progressive MS, apart from some preliminary and modest effects with ocrelizumab for PPMS, treatment is essentially confined to symptom management (Feinstein, Freeman, & Lo, 2015)

1.1.7   Prognosis

Neurological disability is objectively measured using the Expanded Disability Status Scale (EDSS Kurtzke, 1983). The EDSS is rated between 0 (no disability) and 10 (death due to MS) with higher scores indicating greater neurological disability. The scale assess eight functional systems that include pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral and other. Rating is primarily dependent on physical disability and does not take into consideration mood and affective disorders. The EDSS is commonly used in clinical trials as a disability outcome measure.

There is considerable variability in long-term outcomes in MS. Factors associated with faster time to irreversible disability include male gender, older age at disease onset, motor symptoms at onset, progressive disease course, poor recovery from the first relapse, and shorter time between onset of MS and second neurological attack (Amato & Ponziani, 2000; Confavreux, Vukusic, & Adeleine, 2003; Vukusic & Confavreux, 2003). Some studies have also suggested that

8

the number of relapses experienced within the first 5 years after disease onset is predictive of sooner progression to irreversible disability (Christian Confavreux et al., 2003; Kantarci et al., 1998; Tremlett et al., 2009), but recent studies indicate that the effect results primarily from the first 2 years (Leray et al., 2010; Scalfari et al., 2010, 2013; Sormani et al., 2011). An alternative view is that the capacity to achieve remission after a relapse rather than the number of relapses may have greater prognostic value (Amato & Ponziani, 2000; Scalfari et al., 2010). The median time to progression of having to use assistive devices for walking and to a wheelchair is 18 years and 28 years from disease onset, respectively (Leray et al., 2010; Scalfari et al., 2010)

1.2 Cognitive Impairment in Multiple Sclerosis

Observations of cognitive difficulties in MS date back to Charcot (1868) who noted "marked enfeeblement of the memory, conceptions are formed slowly and intellectual and emotional faculties are blunted in their totality." It would, however, take more than a hundred years before a more complete picture of cognitive dysfunction became better known and widely accepted.

1.2.1 Prevalence

Due to the heterogeneous nature of disease progression in MS, the prevalence of cognitive impairment can vary anywhere from 40% to 70%. A seminal paper by Rao, Leo, Bernardin, & Unverzagt (1991) explored the prevalence of cognitive impairment in a sample of 100 community-based MS patients and 100 demographically matched healthy controls. Based on a comprehensive neuropsychological battery that consisted of 31 cognitive indices, 48% of

9

people with MS versus 5% of healthy controls were found to be impaired on 4 or more measures. Community-based samples are characterized largely by relapsing-remitting disease and low neurological disability and cognitive impairment is found in roughly 35-45% of individuals (Duquin, Parmenter, & Benedict, 2008; Patti et al., 2009). In clinic-based samples which contain a larger portion of people with SPMS and PPMS, the prevalence of cognitive impairment can be as high as 60-70% (Benedict et al., 2006; Duquin et al., 2008; Potagas et al., 2008). The specific cognitive domains impacted vary between individuals, however, deficits in information processing speed and learning and memory are the most common. Executive functioning, visuospatial processing, and language are also affected, but to a lesser extent.

1.2.2 Information Processing Speed

Slowness in information processing speed is the primary cognitive deficit observed and affects approximately 30-50% of people with MS (Akbar, Honarmand, Kou, & Feinstein, 2011; Benedict et al., 2006; DeLuca, Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004; Denney, Lynch, Parmenter, & Horne, 2004; Lapshin, Lanctôt, O'Connor, & Feinstein, 2013; Strober, Rao, Lee, Fischer, & Rudick, 2014). As a result of this deficit, other cognitive domains, for example executive functioning, are also impacted since speed of information processing is a component in task performance. Indeed studies have found positive correlations with deficits in processing speed and extent of memory impairment (Janculjak, Mubrin, Brinar, & Spilich, 2002; Lengenfelder, Chiaravalloti, Ricker, & DeLuca, 2003). In addition processing speed is found to be predictive of performance on measures of everyday life activities (Kalmar, Gaudino, Moore, Halper, & Deluca, 2008).

The Paced Auditory Serial Addition Test (PASAT) is one of the most commonly used measures of information processing speed and people with MS perform persistently poorer than healthy individuals (Rosti, Hämäläinen, Koivisto, & Hokkanen, 2007). In addition to processing speed, the PASAT also taps into working memory, sustained attention and divided attention. Despite excellent sensitivity and reliability, the PASAT is a difficult task that can induce anxiety in people with MS thereby compromising performance (Aupperle, Beatty, Shelton, & Gontkovsky, 2002). It is also susceptible to practise effects (Barker-Collo, 2005; Nagels, D'hooghe, Kos, Engelborghs, & De Deyn, 2008).

The SDMT is another sensitive measure of information processing speed commonly used in MS. The test was originally developed by Smith (1982), but revised by Rao and colleagues in 1991 for use in people with MS (Rao, 1990). Unlike the PASAT, performance on the SDMT requires a larger processing speed component and little working memory, and the test makes no demands on math skills. It is relatively quick and easy to administer and does not induce performance anxiety. Studies have shown the SDMT to be more reliable and sensitive compared to the PASAT (Benedict et al., 2008; Benedict et al., 2006). For these reasons, it has been suggested that the SDMT replace the PASAT as the single cognitive measure on the Multiple Sclerosis Functional Composite (MSFC; Drake et al., 2010)

1.2.3 Learning and Memory

Alongside processing speed, learning and memory deficits are also frequent in people with MS. Visual memory is commonly assessed using the Brief Visuospatial Memory Test – Revised (BVMT-R) or the 10/36 spatial recall test. Approximately 30-54% of people with MS are found to have deficits in visual memory (Benedict et al., 2006; Dusankova, Kalincik, Havrdova, &

Benedict, 2012; Feinstein, Lapshin, & O'Connor, 2012). Verbal memory is impaired in 20-30% of people with MS. It is commonly assessed using the California Verbal Learning Test – II (CVLT-II) or the Selective Reminding Test (SRT). Deficits in immediate and delayed recall are found to be equally prevalent.

Early studies suggested that memory deficits were primarily due to problems with retrieval rather than encoding (Beatty, Goodkin, Monson, Beatty, & Hertsgaard, 1988). A later theory proposed that difficulty in encoding information is responsible for verbal memory deficits and acquisition and storage problems contribute to visual memory deficits (DeLuca, Gaudino, Diamond, Christodoulou, & Engel, 1998). On verbal memory tasks, MS subjects require more trials to learn the information, but after acquiring this information their delayed memory is comparable to that of healthy controls.

Working memory refers to the cognitive framework involved in the temporary storage and manipulation of information required to perform various tasks (Baddeley, 1986). Visual information is temporarily stored in the 'visuospatial sketchpad' and auditory information in the 'phonological loop.' The central executive located in the prefrontal cortex is responsible for coordinating and integrating this information. Studies suggest that deficits in working memory are due to problems with the central executive (Lengenfelder et al., 2006, 2003). This is evident in people with MS based on their poor performance on the PASAT where information has to be stored and manipulated.

1.2.4 Executive Functioning

Executive functioning refers to a wide range of cognitive processes and behaviors such as problem solving, abstract thinking, decision making, planning, and inhibition of habitual responses, to name a few. Common tasks used to assess executive functioning in MS include the Wisconsin Card Sorting Test (WCST) and the sorting test that is part of the Delis-Kaplan Executive Function System (D-KEFS). The prevalence of executive dysfunction is reported to be 15-26% (Benedict et al., 2006; Drew, Tippett, Starkey, & Isler, 2008; Foong et al., 1997). In addition to card sorting tests, verbal fluency tests which include both phonemic and semantic fluency, have an executive component to them.

1.2.5 Visuospatial Processing

The prevalence of visuospatial deficits in MS is 18-26% when assessed with the judgement of line orientation task (Benedict et al., 2006; Dusankova, Kalincik, Havrdova, & Benedict, 2012; Vleugels et al., 2000). In addition, deficits on a number of visuoperceptual tasks, such as object recognition, facial recognition, and colour discrimination have been reported (Vleugels et al., 2001). Of note is that visuospatial deficits have been shown to occur independent of problems with visual acuity or neurological disability.

1.2.6 Verbal Fluency

Approximately 10-23% of MS subjects are found to be impaired on tests of verbal fluency, with similar rates for phonemic and semantic fluency (Benedict et al., 2006; Dusankova et al., 2012; Henry & Beatty, 2006). The Controlled Word Oral Association Test (COWAT) is a widely used measure of verbal fluency in MS. One caveat of verbal fluency tests is that they probe more than executive function, tapping into information processing speed and working memory as

well (Salthouse, Atkinson, & Berish, 2003; Zakzanis, 2000). Given that slowness in information processing speed affects approximately 50% of people with MS, coupled with the fact that verbal fluency tests are timed, it becomes difficult to tease out the specific aspect of cognition that influences task performance.

1.3 Correlates of Cognitive Impairment in MS

1.3.1 Disease Related Factors

Several disease related factors, including disease course, duration of disease, and physical disability, have been associated with cognitive impairment in MS. Studies have shown cognitive impairment to be more severe in subjects with PPMS and SPMS than RRMS (Comi et al., 1995; De Sonneville et al., 2002; Denney, Sworowski, & Lynch, 2005; Huijbregts et al., 2004, 2006; Olivares et al., 2005; Potagas et al., 2008). In addition to severity of cognitive impairment, the specific cognitive domains affected may also vary between the three disease subtypes. Individuals with RRMS perform better on tasks of information processing speed (PASAT and SDMT) than those with SPMS and PPMS, whereas RRMS and SPMS subjects perform significantly worse than PPMS subjects on tests of visuospatial processing and verbal fluency (De Sonneville et al., 2002; Huijbregts et al., 2006). Important to note, however, is that the relationship between disease course and severity of cognitive impairment may weaken after controlling for age, physical disability and disease duration (Henry & Beatty, 2006; Potagas et al., 2008). This is not surprising given the fact that subjects with a progressive disease course tend to be older, have a greater duration of disease and increased physical disability.

Most cross-sectional studies report either a weak or absent correlation between cognitive impairment and disease duration (Lynch, Parmenter, & Denney, 2005; Patti et al., 2009). Studies show approximately 20-50% of individuals with benign MS or CIS having cognitive difficulties (Feuillet et al., 2007; Glanz et al., 2007; Potagas et al., 2008; Zipoli et al., 2010). A few longitudinal studies have examined the pattern of cognitive changes over time and conflicting results have been reported. Studies with follow-up periods of less than 5 years report either little change in cognitive status over time or progressive deterioration in a subset of individuals (Amato et al., 1995, 2010; Amato, Zipoli, & Portaccio, 2006; Denney, Lynch, & Parmenter, 2008; Feinstein, Kartsounis, Miller, Youl, & Ron, 1992; Kujala, Portin, & Ruutiainen, 1997; Patti, Failla, Ciancio, L'Episcopo, & Reggio, 1998; Reuter et al., 2011). With longer follow-up periods of 10 or more years a different picture emerges. Amato et al. (2001) examined cognitive and neurological changes 10 years after baseline assessment and found that over the decade the prevalence of cognitive impairment in their sample increased from 26% to 56%. A more recent 18 year follow-up study reported significant cognitive decline over time on measures of information processing speed, attention, episodic learning and memory and visual construction (Strober, Rao, Lee, Fischer, & Rudick, 2014).

Early studies have either failed to find any association or report a weak correlation between cognitive measures and physical disability (Beatty et al., 1990; Rao et al., 1991; van den Burg, van Zomeren, Minderhoud, Prange, & Meijer, 1987). Relatively recent studies contradict findings of earlier studies. Patti et al. (2009) reported on 550 MS subjects with a relapsing-remitting disease course and mild disability and found that cognitively impaired subjects had higher EDSS scores than those who were intact. Furthermore, the EDSS was found to correlate,

albeit weakly, with performances on individual cognitive tests. Similarly, Lynch, Parmenter, & Denney (2005) also reported significant correlations between several cognitive measures (information processing speed, verbal fluency, learning and memory and executive functions) and physical disability. Longitudinal studies have also documented this association. In a 4 year follow-up study, Amato et al. (1995) found disability, based on the EDSS, correlated with only 4 out of 13 cognitive measures, but in a subsequent re-examination of their original subjects at 10 years they found age, EDSS and progressive disease course to be significantly associated with cognitive decline (Amato et al., 2001). These findings have been replicated by recent studies (Bergendal, Fredrikson, & Almkvist, 2007; Schwid, Goodman, Weinstein, McDermott, & Johnson, 2007) and suggest that as the disease progresses, there is a convergence of neurological and cognitive deficits. Overall, it is difficult to tease out a clear connection between cognitive impairment and disease duration, disease course and physical disability as there is significant overlap between these factors. Furthermore, substantial variation exists among people.

1.3.2   Depression

The life time prevalence of depression in MS is approximately 50%, which is significantly higher than that found in the general population (Patten, Beck, Williams, Barbui, & Metz, 2003; Sadovnik et al., 1996). A recent longitudinal study has also reported that depressive symptoms in MS remain relatively stable over the years, suggesting that depression is a chronic problem in MS (Koch et al., 2015). Early studies failed to find a relationship between depression and cognitive functioning (Good, Clark, Oger, Paty, & Klonoff, 1992; A. Moller, Wiedemann, Rohde, Backmund, & Sonntag, 1994). This, however, could have been due to methodological

limitations such as small sample sizes, the use of depression rating scales confounded by symptoms of fatigue and sleep, and the use of neuropsychological tests lacking sensitivity. In addition, correlational analyses were primarily used to investigate the relationship, but depression effects on cognition may not be linear. A certain threshold for mood disturbance may be required before cognitive effects are observed. Keeping in mind these limitations, Arnett et al. (1999) compared the cognitive performance of three distinct groups (MS subjects with depression, MS subjects without depression and healthy controls without depression) on an effortful test of working memory. Their results suggested that depressed MS subjects have a limited working memory capacity, which allows them to allocate fewer attentional resources towards capacity demanding tasks such as those involved in information processing speed and executive functions. Similarly, Demaree, Gaudino, & DeLuca (2003) demonstrated how cognitive capacity was a function of depression severity by comparing cognitive performance on the Selective Reminding Test (SRT) and the PASAT between three groups, namely MS subjects with mild depression, MS subjects with severe depression and healthy controls. Their results indicated that the greatest deficits were to be found in the severely depressed MS group.

1.3.3   Anxiety

The lifetime prevalence of anxiety in the MS population is found to range between 30 to 60% (Akbar, Honarmand, & Feinstein, 2011; Beiske et al., 2008; Bruce & Arnett, 2008; Korostil & Feinstein, 2007; Simioni, Ruffieux, Bruggimann, Annoni, & Schluep, 2007). In contrast to the literature on depression, very few studies have looked at the relationship between anxiety and cognitive functioning in MS. Anxiety has been found to be more prevalent in people with

cognitive impairment (Simioni et al., 2007) and more specifically it has been correlated with performance on tasks of executive functioning (Stenager, Knudsen, & Jensen, 1994). Julian & Arnett (2009) further explored the relationship between anxiety and executive functioning and concluded that state, but not trait anxiety predicted performance on a task of executive functioning independent of depression. In addition, a recent study has also found that state anxiety is related to poorer performance on tasks of information processing speed (Goretti et al., 2014). Although the number of studies are limited, evidence suggests that anxiety influences cognitive performance to some extent.

1.3.4 Fatigue

Fatigue has been reported in 50 to 80% of people with MS, profoundly disrupting their quality of life, relationships, leisure pursuits, and the ability to function at work (Strober, 2015; Benito-León et al., 2007; Kaynak et al., 2006; Lerdal, Celius, Krupp, & Dahl, 2007; Lerdal, Celius, & Moum, 2003; Morrow, Weinstock-Guttman, Munschauer, Hojnacki, & Benedict, 2009; Stanton, Barnes, & Silber, 2006). Moreover, more than 50% of people have reported fatigue as their most severe symptom. Primary fatigue is thought to be mediated by the disease process, whereas secondary fatigue is the result of co-morbid conditions commonly associated with MS such as sleep and mood disturbances (DeLuca, 2005). The subjective nature of fatigue, however, has led clinicians and researchers to define it differently. For example, The UK Multiple Sclerosis Society defines MS related fatigue as "an overwhelming sense of tiredness for no apparent reason" whereas the Multiple Sclerosis Council for Clinical Practice Guidelines defines fatigue as "a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities." A clear definition is

18

difficult to formulate for fatigue given that it is a multidimensional construct involving physical, cognitive and psychosocial components.

The relationship between fatigue and cognitive functioning in MS is unclear. Significant associations have been found between self-reported fatigue and perceived cognitive deficits (Parmenter, Denney, & Lynch, 2003). Using objective neuropsychological measures, some researchers have reported significant associations with fatigue (Diamond, Johnson, Kaufman, & Graves, 2008), whereas others have not (Beatty et al., 2003; Kinsinger, Lattie, & Mohr, 2010; Morrow et al., 2009). Cognitive fatigue, which is described as a decrease in performance during sustained mental effort, has also been objectively quantified on the PASAT and found to significantly impact MS subjects, but not healthy controls (Schwid et al., 2003). Furthermore, alleviation of fatigue with treatment does not improve objective neuropsychological performance, but it does influence perceived cognitive deficits (Kinsinger et al., 2010)

Considerable attention has been given to sleep disturbances as a cause for MS related fatigue. Sleep disorders reported in MS include restless leg syndrome, periodic limb movement, narcolepsy, rapid eye movement behaviour disorder, insomnia, and obstructive sleep apnea (see Kaminska, Kimoff, Schwartzman, & Trojan, 2011 for review). The prevalence of sleep disorders is higher in MS than the general population, with reports suggesting anywhere between 19 to 67% of people experiencing some sort of sleep disturbance (Brass, Duquette, Proulx-Therrien, & Auerbach, 2010; Brass, Li, & Auerbach, 2014; Kaynak et al., 2006; Merlino et al., 2009; Strober, 2015). A large MS study assessing subjective sleep quality in community populations reported that 13.3% of people had mild, 21.5% moderate and 30% severe sleep difficulties (Bamer et al., 2008). A number of studies have found a significant association

between sleep disturbance and fatigue in MS (Kaminska et al., 2012; Kaynak et al., 2006; Stanton et al., 2006; Strober, 2015)

No studies to date have looked at the association between sleep and cognitive dysfunction in MS. In the general population, individuals with sleep related breathing disorders and narcolepsy are found to have reduced performance on tasks of attention compared to healthy controls (Fulda & Schulz, 2001). These individuals are also found to have impaired driving performance on a simulated test. Given that sleep disturbances and excessive daytime sleepiness are common in MS, these factors could potentially explain additional variance in cognitive performance beyond that accounted for by fatigue and depression.

1.3.5   Neuroimaging Markers

Structural

Using techniques such as magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), and magnetization transfer imaging (MTI), studies have shown a significant association between cognitive impairment and brain pathology. Cognitive impairment in MS has been associated with total T_2 lesion volume, brain atrophy, and changes in normal appearing brain tissue.

Greater T_2 and T_1 lesion loads have been found in cognitively impaired versus intact people with MS (Calabrese et al., 2009; Lazeron et al., 2005). This has been found for both white matter, as well as cortical and subcortical gray matter lesions (Moraal et al., 2009). Regional lesion volumes have also been linked to specific cognitive failings. For instance, a higher frontal lobe lesion is associated with impaired executive functions (Foong et al., 1997), whereas lesions in

the parieto-occipital lobe have been associated with deficits in verbal learning and visuospatial skills (Bagnato et al., 2010; Sperling et al., 2001; Swirsky-Sacchetti et al., 1992)

The most recent studies have shown brain atrophy to be more strongly associated with cognitive impairment than lesion load. In an MRI investigation of 37 MS subjects, Benedict et al. (2004) found central brain atrophy (measured by third ventricular width) to be strongly associated with neuropsychological performance, even after controlling for age, premorbid intelligence and depression. After excluding third ventricle width from the regression model, whole brain atrophy (measured by brain parenchymal fraction) was the second best predictor of cognitive performance. Based on these and similar findings by other groups, there is strong evidence that brain atrophy is a more robust predictor of cognitive performance in MS than lesion load (Fisher, Lee, Nakamura, & Rudick, 2008; Sánchez, Nieto, Barroso, Martín, & Hernández, 2008). The strong association between third ventricular enlargement and cognitive performance has been attributed to atrophy of the thalamus, a sensory relay station for information traveling to and from the cerebral cortex (Houtchens et al., 2007). In addition, there is a significant association between neocortical volume and performance on neuropsychological tests (Amato et al., 2007; Batista et al., 2012). With respect to white matter, atrophy of the corpus callosum has been associated with performance on tests of information processing speed and visual memory (Roosendaal et al., 2009; Sánchez et al., 2008). Finally, changes in normal appearing grey and white matter, as detected by DTI and MTI, are also implicated in cognitive impairment. Benedict et al. (2013) showed that DTI measures, specifically mean diffusivity and fractional anisotropy within the thalamus, explain additional variance in predicting cognitive impairment after controlling for the effects of thalamic volume.

Functional MRI

Functional MRI studies suggest that MS subjects: 1) show increased activation of brain regions involved in task performance (Rocca et al., 2010; Rocca et al., 2014) and 2) recruit additional neural networks typically not activated in healthy controls (Audoin et al., 2008; Forn et al., 2007; Genova, Hillary, Wylie, Rypma, & Deluca, 2009). These compensatory activation patterns are found to decrease with increasing task difficulty, indicating that beyond a specific threshold, functional adaptations may not preserve cognitive abilities (Penner, Rausch, Kappos, Opwis, & Radü, 2003). A loss of this compensatory mechanism due to extensive pathological damage is associated with cognitive impairment. Individual variation in functional adaptability after brain damage is discussed further in the cognitive reserve section.

1.3.6 Genetic Factors

In a search for genetic correlates of cognitive impairment, the focus has fallen on apolipoprotein E (APOE) and genetic variations in brain derived neurotrophic factor (BDNF). Despite some equivocal data, the current consensus is that there is no association between cognitive impairment and the APOE ε4 allele (Ghaffar & Feinstein, 2010). In a study that explored the relationship between cognition, structural brain imaging including DTI and the APOE ε4 allele, a significant association was found between the imaging and cognitive indices, but not linked to the genetic marker. The BDNF data are however different, with polymorphisms associated with deficits in information processing speed and working memory (see Benedict & Zivadinov, 2011 for review).

1.4 Treatment for Cognitive Impairment in MS

Treatment options for cognitive impairment in MS include pharmacological and non-pharmacological interventions.

1.4.1 Pharmacological Interventions

A review of pharmacological agents reveals failed studies for potassium channel blockers (Rossini et al., 2001), amantadine (Geisler et al., 1996), and modafinil (Moller et al., 2011). Some weakly positive findings have been reported with disease modifying drugs (DMDs) and stimulants. The drugs used to treat cognition in Alzheimer's disease, namely acetylcholinesterase inhibitors, are not effective in MS.

Findings on the effects of DMDs are limited since cognition in clinical trials is generally a secondary outcome, focusing primarily on PASAT performance. In subjects with RRMS, treatment with interferon-B-1b has shown modest effects on information processing speed and learning and memory (Barak & Achiron, 2002; Kappos et al., 2009). A large study by the European Study Group with 718 SPMS subjects showed no beneficial effects on any cognitive measure (European Study Group, 1998). Positive treatment effects of interferon-B-1a have also been reported (Patti et al., 2010). A recent pilot study has suggested that natalizumab may reduce cognitive decline in people with RRMS (Portaccio et al., 2013).

Acetylcholinesterase inhibitors (AChEIs) such as donepezil, rivastigmine, and galantamine, have previously been used to treat cognitive deficits in Alzheimer's and Parkinson's disease. An early study reported a positive treatment effect of donepezil on memory based on the selective reminding test (Krupp et al., 2004). However, these findings were not replicated in a more

recent clinical trial with a larger sample size (Krupp et al., 2011). Similarly, negative results have been reported with rivastigmine.

Two recent studies have shown the potential of amphetamines in improving cognitive functions in MS, especially information processing speed. Benedict et al. (2008) reported the effects of l-amphetamine on measures of information processing speed. In this study, 19 MS subjects were split into 4 treatment conditions, namely placebo, 15, 30 and 45 mg of l-amphetamine dosage. Significantly higher scores on the PASAT and SDMT were seen in the 30 and 45mg groups compared to placebo and those receiving 15mg l-amphetamine. Improvements in memory function have also been reported with amphetamine treatment (Sumowski et al., 2011).

1.4.2 Cognitive Rehabilitation

A complimentary approach to treatment is cognitive rehabilitation. A couple of Cochrane reviews are not enthusiastic, but there are some promising findings from a few individual studies. In particular, learning and memory has been the focus of several interventions. Targeted intervention techniques that have shown to be effective in improving learning and memory include spaced learning (a technique where learning trials are spaced out over time), self-generated learning (whereby people generate their own concepts to learn words rather than being told what to remember), and use of context and imagery. The latter was recently assessed in a randomized control trial in which a modified Story Memory Technique improved learning and memory in people with MS (Chiaravalloti, Moore, Nikelshpur, & Deluca, 2013). In addition to specific targeted interventions, non-specific cognitive training, such as home-based computer assisted training, is also found to be beneficial in improving learning and memory (Hildebrandt et al., 2007).

24

Unlike learning and memory, no behavioral interventions have specifically targeted information processing speed, despite it being the most common cognitive deficit in people with MS. Non-specific cognitive training using computers has shown moderate effects at improving scores on the PASAT (Hildebrandt et al., 2007; Mattioli, Stampatori, Zanotti, Parrinello, & Capra, 2010). Computerized cognitive training has also shown benefits in executive functions, working memory, and attention (Brenk, Laun, & Haase, 2008; Fink et al., 2010; Goverover, Chiaravalloti, & Deluca, 2008).

Functional MRI (fMRI) investigations have shown that improvements in cognition with cognitive rehabilitation are associated with improved fMRI brain metrics. A recent study showed enhanced activity in the posterior cingulate cortex and dorsolateral prefrontal cortex following cognitive rehabilitation using computers (Filippi et al., 2012). Compared to the control group which received no rehabilitation, the treatment group showed significant improvements in information processing speed, attention and executive functions. Similarly, Chiaravalloti et al. (2012) showed increased cerebral activation in frontal, parietal and parahippocampal regions after behavioral treatment with the Story Memory Technique. Overall, despite inconsistent results from early studies, recent investigations suggest possible benefits of cognitive rehabilitation on neuropsychological performance.

1.5 The Impact of Cognitive Impairment on Daily Life and Disease Outcome

Individuals with cognitive impairment have difficulty finding and sustaining employment, pursuing leisure activities, and completing daily household task (Goverover, Genova, Hillary, & DeLuca, 2007; Rao, Leo, Ellington, et al., 1991). They also report greater sexual dysfunction.

These difficulties cannot be explained by depression, anxiety or physical disability alone. Using an objective measure of functional status, the Executive Function Performance Test (EFPT), Kalmar et al., (2008) reported that individuals with cognitive impairment required greater assistance in completing the EFPT. Similarly, Kessler et al. (1992) reported that functional impairment based on the Activities of Daily Living Scale and objective performance on sensorimotor tests, was associated with memory dysfunction.

The ability to drive is an important factor that gives individuals a sense of autonomy. Studies have shown that MS subjects with cognitive impairment perform significantly worse on driving related tests than those who are intact and healthy control subjects (Schultheis, Garay, & Deluca, 2001; Schultheis, Garay, Millis, & DeLuca, 2002). More specifically, information processing speed is found to be a strong predictor of driving performance based on the clinical behind-the-wheel driving evaluation. Visuospatial learning and recall are strong predictors of collision and driving violation frequency (Schultheis et al., 2010).

Given that MS typically affects middle-aged adults, many who are just beginning to rise in their careers, the most debilitating consequence of cognitive impairment may be loss of employment. Approximately 40-80% of people with MS are unemployed, with the majority becoming unemployed within 10 years of diagnosis (Gronning, Hannisdal, & Mellgren, 1990; Kornblith, LaRocca, & Baum, 1986; Morrow et al., 2010; Strober et al., 2012). Unemployment is largely attributed to cognitive deficits (Honarmand, Akbar, Kou, & Feinstein, 2011), since demographic factors and physical disability account for less than 14% of the variance in employment status (Larocca, Kalb, Scheinberg, & Kendall, 1985). Furthermore, Beatty et al. (1995) reported that almost half of the variance in employment status is accounted for by

walking ability, age, and three measures of cognitive functioning. Difficulty in sustaining

employment has been particularly attributed to deficits in information processing speed,

memory and executive functions (Benedict et al., 2005; Strober et al., 2012; Morrow et al.,

2010). These three cognitive domains predict vocational status even after adjusting for

demographic (age, gender, years of education), neurologic (disease course, disease duration,

physical disability), and psychiatric (depression, anxiety) factors (Benedict et al., 2006). Overall,

the impact of cognitive dysfunction on employment and activities of daily living significantly

reduces the quality of life for individuals with MS.

In addition to the above factors, cognitive impairment also has an important prognostic value in

disease outcomes. For instance, cognitive impairment in individuals with CIS is predictive of

early conversion to clinically definite multiple sclerosis (Zipoli et al., 2010). Furthermore,

pronounced deficits in information processing speed and verbal memory early in the disease

significantly correlate with worsening physical disability 5 and 7 years later (Deloire, Ruet,

Hamel, Bonnet, & Brochet, 2010). Individuals with cognitive impairment are also found to have

a compromised response to cognitive rehabilitation, poorer adherence to treatment and

greater vulnerability to psychiatric conditions such as depression and anxiety.

1.6 Detecting Cognitive Impairment

Given the far-reaching consequences of cognitive impairment in MS, detection becomes vital so

that individuals can seek therapy, and if necessary, adjust their lifestyle to compensate for their

difficulties. Both comprehensive and brief assessment tools, encompassing an array of tests

sensitive to cognitive deficits commonly observed in MS, have been developed for clinical and research purposes.

1.6.1 Minimal Assessment of Cognitive Functioning in MS (MACFIMS)

The Minimal Assessment of Cognitive Functioning in MS (MACFIMS) is a consensus derived battery of tests, developed in 2001 by a panel of experts in the field of neuropsychology (Benedict et al., 2002). The MACFIMS is a comprehensive assessment tool consisting of seven tests assessing five cognitive domains. The tests that make up the battery are described in greater detail in the methods section of this thesis. To summarize briefly, the MACFIMS includes: 1) information processing speed – Paced Auditory Serial Addition Test (PASAT) and Symbol Digit Modalities Test (SDMT), 2) learning and memory – California Verbal Learning Test – II (CVLT-II) and Brief Visuospatial Memory Test – Revised (BVMT-R), 3) executive functions – Delis-Kaplan Executive Functioning System (D-KEFS) Sorting Test, 4) visuospatial processing – Judgement of Line Orientation (JLO) test and 5) verbal fluency – Controlled Oral Word Association Test (COWAT). The MACFIMS takes approximately 90 minutes to administer and has been previously validated for use in people with MS (Benedict et al., 2006). In addition to strong sensitivity and reliability, the comprehensiveness of the MACFIMS battery allows clinicians to obtain a broad neuropsychological profile. However, the length of the battery means that it cannot be used in a busy clinical setting.

1.6.2 Brief Screening Batteries

Given time constraints in many settings, shorter assessment tools have been developed to screen for cognitive deficits. These include the Brief Repeatable Battery of Neuropsychological Tests (BRB-N) and the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS).

The BRB-N comprises of the Selective Reminding Test as a measure of verbal memory, the 10/36 Spatial Recall Test for visuospatial memory, the COWAT for verbal fluency, and the PASAT and SDMT for information processing speed and working memory (Rao, 1991). The BRB-N takes approximately 40 minutes to administer and has comparable sensitivity to the comprehensive MACFIMS battery (Strober et al., 2009). There are 15 alternate versions available, which allows repeatable assessments with minimized influence of practice effects. The tests also have been widely translated.

More recently, an expert panel of neurologists and neuropsychologists with experience in research and clinical care of MS, recommended an even briefer screen for cognition, the BICAMS. The BICAMS includes the SDMT, the CVLT-II – first five recall trials, and the BVMT-R – first three recall trials (Langdon et al., 2012). The BICAMS takes approximately 15 minutes to complete and comparisons have been undertaken with the MACFIMS. In a sample of 367 MS subjects, the sensitivity and specificity of the BICAMS in detecting global cognitive impairment relative to the MACFIMS was assessed (Dusankova et al., 2012). Impairment on at least 1 out of 3 cognitive indices on the BICAMS resulted in the highest sensitivity and specificity (94% and 86%, respectively) and both batteries had similar rates of cognitive impairment (BICAMS: 58% and MACFIMS: 55%). Recent Canadian data reports the BICAMS to be a reliable and valid measure of cognition in MS (Walker et al., 2016). Further validation studies with the BICAMS are currently underway.

1.6.3   The Symbol Digit Modalities Test (SDMT) – A Single Sensitive Measure

Despite availability of brief cognitive screening tools, the search continues for a single most sensitive measure of cognition that can be quickly and easily administered in clinical settings.

Given that deficits in information processing speed are common and considered the quintessential cognitive deficit in MS, the focus has fallen here. In particular, the SDMT is known to have good sensitivity (Akbar, Honarmand, Kou, et al., 2011; Van Schependom et al., 2014), excellent reliability (Benedict et al., 2008) and is known to correlate robustly with MRI brain metrics (Batista et al., 2012; Papadopoulou et al., 2013). It does not induce anxiety, like the PASAT does, and as such, it has been recommended to replace the PASAT as part of the MSFC. The MSFC is a neurological outcome measure that assess motor functioning in the upper and lower extremities and cognitive functioning with the 3 second PASAT. Drake et al. (2010) compared two versions of the MSFC, one with the PASAT and the other with the SDMT. Their results showed that although the two versions had roughly equal validity, the SDMT version was slightly better at differentiating MS subjects from healthy controls and predicting vocational status. Overall, the extensive literature on the SDMT suggests it to be a quick, sensitive and reliable measure for screening cognitive impairment.

1.7 Current Limitations in Detecting Cognitive Impairment

Despite the extensive research done on developing sensitive measures for detecting cognitive impairment in MS, challenges remain that hinder the availability and validity of neuropsychological testing. These include accessibility to neuropsychologists, time constraints that impede ease of access in a clinical setting, sensitivity in detecting subtle cognitive deficits in individuals with a high cognitive reserve and lack of ecological validity.

30

1.7.1 Accessibility and Time

Accessibility to neuropsychological services is difficult for many people, especially those living in rural areas. The referral for neuropsychological testing generally comes from a neurologist, but approximately 25-33% of individuals with MS do not see a neurologist on a yearly basis (Minden, Frankel, Hadden, & Hoaglin, 2007). These individuals are likely to have a lower income, longer duration of illness, disability and live in rural areas (United States data). Additionally, the paucity of neuropsychologists in Canada further restricts accessibility even after a referral is obtained (Hayman-Abello, Hayman-Abello, & Byron, 2003)

The shortest battery of cognitive tests recommended, the BICAMS, takes at least 15 minutes to complete and in busy hospital based clinics even this much time may be difficult to allot. The authors of the BICAMS recommend that when only a few minutes are available for testing, the choice should fall to the SDMT (Langdon et al., 2012).

Computerized cognitive testing has been suggested as one possible solution to the problem of accessibility. Potential advantages of computerized tests include easy administration that does not require a trained psychometrician, automated data collection and excellent reliability.

1.7.2 The Influence of Cognitive Reserve

In the geriatric population, several cases have been described of individuals who were cognitively intact, but found to have Alzheimer's disease on autopsy (Katzman et al., 1989). This suggests that brain pathology does not always lead to the clinical manifestation of that damage and the concept of reserve has been proposed to explain this variability. Cognitive reserve has been defined as "individual differences in cognitive processing that allows some people to cope

31

better than others with brain damage" (Stern, 2002, 2009). This can involve more efficient use of networks typically involved in processing a task or recruitment of alternate networks. Compared to individuals with low cognitive reserve, those with high reserve show less task-related brain activation and require higher levels of task difficulty before recruiting alternate brain regions (Rympa, Prabhakaran, Desmond, Glover, & Gabrieli, 1999). Overall, those individuals who have more efficient cognitive processing and are able to recruit alternate networks with increasing demands, can better tolerate brain damage.

Cognitive reserve is determined by occupational attainment (Stern, Tang, Denaro, & Mayeux, 1995; Stern, Alexander, et al., 1995), level of education (Elkins et al., 2006; Mortel, Meyer, Herod, & Thornby, 1995), premorbid leisure activity (Scarmeas, Levy, Tang, Manly, & Stern, 2001; Scarmeas et al., 2003; Verghese et al., 2003) and premorbid IQ (Alexander et al., 1997; Sumowski, Wylie, Chiaravalloti, & DeLuca, 2010). Of these, premorbid IQ based on verbal vocabulary knowledge, is found to be a particularly strong measure, however, studies have shown independent contributions of occupational attainment, leisure activity and education to cognitive reserve.

The influence of cognitive reserve has primarily been investigated in Alzheimer's disease and the general aging literature. However, recent studies have shown its neuroprotective role in MS as well. Sumowski et al. (2009; 2013) demonstrated the protective influence of high cognitive reserve (measured using premorbid IQ) on tasks of complex information processing speed and verbal learning and memory. In addition, high cognitive reserve was found to attenuate the effects of cerebral atrophy on cognition. Cognitive leisure activity has also been found to

independently contribute to cognitive status in MS (Sumowski, Wylie, Gonnella, Chiaravalloti, & Deluca, 2010)

Despite its beneficial effects, individuals with high cognitive reserve may not be completely shielded from cognitive deterioration. In general, individuals with high cognitive reserve work in more intellectually demanding jobs. Thus, even a small fall-off in cognition can have significant work related consequences even in the context of neuropsychological results in the normal range. This was shown by Feinstein et al. (2013) in a group of individuals who were found to be cognitively intact on conventional neuropsychological testing, but had deficits relative to their premorbid intellectual abilities. Using a validated algorithm, verbal fluency scores were predicted based on premorbid IQ and compared with actual verbal fluency scores. Overall, 31.3% of MS subjects were found to be cognitively intact on the MACFIMS, but fell short of their predicted verbal fluency scores. Compared to cognitively impaired subjects, this group had a higher premorbid IQ. However, half the subjects were unemployed.

1.7.3 Ecological Validity

Current testing is usually done in the quiet psychometricians' office, usually with a "do not disturb" sign posted outside the door to limit the influence of extraneous noise. This type of setting does not reflect the distracter filled, real-world environment normally found in the workplace or routine life. As a consequence of this ecological divide, individuals may pass all tests in the quietness of the psychometrician's office, but their cognitive difficulties in the real-world go undetected.

1.8 The Influence of Distracters on Cognition

Efficient cognitive functioning requires the ability to filter out extraneous stimuli in order to concentrate on a task at hand. Distracters from all sensory modalities are present while we carry out daily routines such as driving or functioning at work. The effects of distracters on cognition have been well researched in the general neuropsychological literature in healthy subjects, but not so in people with MS.

1.8.1 Distracter Paradigms Used in Research

Auditory distracters have been of particular interest given their ubiquitous presence and their ability to derail attention. Distracters can be deviant sounds which differ on a single acoustic property from a standard sequence (e.g. change in frequency) or they can be novel sounds that differ on many properties (e.g. environmental noise; Berti, 2012; Escera, Alho, Winkler, & Naatanen, 1998; Schröger, 1996). Visual distracters can be presented in an analogous fashion.

In the real-world, we are usually distracted by events occurring in a different sensory modality than the primary task at hand. To assess this in an experimental setting, cross-modal paradigms have been used that include auditory-visual and tactile-visual distracter (oddball) tasks (see Parmentier, 2014 for methodology review).

Oddball tasks are useful in revealing simple behavioral effects on visual tasks, but this paradigm is further extended by incorporating neuropsychological measures of memory such as serial recall. The *irrelevant sound effect* is the disruption of serial recall of items to be remembered by the presentation of auditory distracters (Beaman & Jones, 1998; R. W. Hughes, Tremblay, & Jones, 2005). In this paradigm, subjects are asked to remember a sequence of visually

presented items (e.g. digits 1 to 9 in a random order) while auditory distracters are interjected during the learning phase. Either standard tones, similar to those in oddball tasks, or irrelevant speech is used as distracter stimuli. When tones are used, differential patterns of auditory distracters, such as steady state sequences (e.g." k k k k" all same frequency), deviation effect (e.g. " a a a b a a a" 1 oddball frequency) or changing state effect (e.g. "k l m n q" all different frequency), can elicit varying magnitudes of result (Hughes, Vachon, & Jones, 2007; Jones & Macken, 1993; Macken, Phelps, & Jones, 2009; Parmentier & Andrés, 2009).

1.8.2   Behavioral Effects of Distracters

Behavioral studies have shown that introducing distracters causes a prolongation of reaction time in responding to target stimuli and decreases accuracy on task performance (Berti & Schröger, 2003; Schröger & Wolff, 1998). These findings extend to auditory, visual, auditory-visual, and tactile-visual oddball tasks. Relatively recent studies, however, suggest that some auditory distracters may facilitate performance on a visual task, whereas others will have negative effects based on the sound's informational value. Parmentier, Elsley, & Ljungberg (2010) used an auditory-visual oddball task to demonstrate that distracter effects (i.e. slowed reaction time and/or decreased accuracy of performance) caused by unexpected sounds are only observable when the sound predicted the occurrence and timing of a visual target. When auditory distracters lost this informational value, no behavioral effects were present. Similarly distracter effects disappear when the occurrence of a sound is predicted by a cued warning (Horváth, Sussman, Winkler, & Schröger, 2011; Shelton, Elliott, Lynn, & Exner, 2009). Behavioral effects are also known to vary depending on whether the distracter is a deviant or novel sound. Presentation of novel environmental sounds results in longer reaction times in responding to a

35

visual target than deviant tones (Berti, 2012; Escera et al., 1998). On a daily basis we encounter environmental sounds more often than deviant sounds, hence their motivational significance could explain why they are more likely to divert our attention.

When auditory distracters are interjected during the learning or retention phase of a verbal memory task, serial recall is significantly impaired relative to the non-distracter condition (Jones, Madden, & Miles, 1992; Röer, Bell, & Buchner, 2014). This impairment is present despite the fact that subjects are told beforehand to ignore any distracters that may appear while the items are presented to them. Furthermore, different patterns of auditory distracters elicit different magnitudes of impairment in serial recall. For example, irrelevant speech that is semantically related to the list of words or items to be recalled is found to be more disruptive than unrelated speech (Marsh, Hughes, & Jones, 2008).

1.8.3   The Duplex Mechanism of Distraction

Two theoretical mechanisms are proposed for auditory distracters, namely interference by process and attentional capture. Interference by process explains the behavioral results of the changing state effect (e.g. k l m n q, all different frequencies) and irrelevant speech. Here the cognitive processing of sound competes with the processing of the primary task, where the changing element of sound or speech is assumed to give cues regarding the order of the sound (Jones & Macken, 1993; Macken et al., 2009). As a result of this simultaneous processing, cognitive performance on the primary task suffers. Relatively minimal or even no distracter effects are seen when steady-state sound sequences are presented because there is no competing cognitive processing of sound order while trying to perform the primary task (Divin, Coyle, & James, 2001). Distraction due to interference by process is evident in the real-world

environment. For example, imagine trying to read an article in a busy coffee shop with several different conversations taking place in the background. In this scenario, an individual may be easily distracted and take in minimal information from their reading material because they are simultaneously trying to process the meaning of words they hear from different conversations taking place while reading.

The second mechanism explaining auditory distraction is attentional *capture*. This is best explained as a brief disengagement of attention away from the primary task towards the distracting stimuli (Escera, Yago, Corral, Corbera, & Nuñez, 2003; Parmentier & Andrés, 2009). It is commonly observed with the deviation effect in experimental settings. Auditory stimuli that are personally salient (e.g. a person's name) or stimuli that disturb recent sensory expectations will divert attention away from the focal task. In the earlier coffee shop example, attentional capture may occur if an individual who is reading hears his or her name being called out (salient auditory stimuli) or if they suddenly hear a loud shriek in midst of normal chatter (deviation from their current auditory expectations).

1.8.4 Reducing Distracter Effects: Top-down vs. bottom-up processes

Experimental evidence has suggested that greater task engagement by increasing task difficulty protects against auditory attentional capture, but not interference by process. Hughes, Hurlstone, Marsh, Vachon, & Jones (2013) increased the difficulty of a serial recall task by embedding the list of words to be remembered in static visual noise. Their results showed that disruption to serial recall by an auditory deviant was eliminated, but distracter effects from a changing-state sequence persisted. The effects of increasing task demands have been explained by top-down (cognitive processing) and bottom-up (perceptual processing) influences. The

37

support for the duplex-mechanism stems primarily from evidence suggesting that top-down control of distractions is only feasible to reduce attentional capture, but has no influence over interference by process (Berti & Schröger, 2003; Berti, 2008; Hughes et al., 2007; Muller-Gass & Schröger, 2007; Poole & Kane, 2009; Rinne, Särkkä, Degerman, Schröger, & Alho, 2006; SanMiguel, Corral, & Escera, 2008; Sörqvist, Marsh, & Nöstl, 2013; Sörqvist, 2010; Weissman, Mangun, & Woldorff, 2002). According to Lavie's load theory (1994), our perception has a limited capacity, meaning that all stimuli in the environment will be processed until perceptual capacity runs out. On this basis, increasing the task complexity maximizes our perceptual processing of the task so that no perceptual capacity remains to process distractions. It has been shown that increasing the perceptual load of the focal visual task attenuates the deviation effect caused by an unexpected sound, but has no effect on the distraction caused by changing state effect (Halin, Marsh, Haga, Holmgren, & Sörqvist, 2014; Hughes et al., 2013; Tellinghuisen & Nowak, 2003).

There are also individual differences in how susceptible individuals are to distraction. Some individuals are able to focus on a task in noisy environments without difficulty, whereas others cannot. One explanation for this is difference in working memory capacity (WMC). WMC is typically measured with complex-span tasks and is an indicator of an individual's top-down cognitive control capacity in reducing distractions (Daneman & Carpenter, 1980). Studies have reported that individuals with high WMC are less likely to be distracted by auditory deviants and irrelevant speech and are less susceptible to distraction in the Stroop task than individuals with low WMC (Conway, Cowan, & Bunting, 2001; Kane & Engle, 2003; Sörqvist, 2010; Tsuchida, Katayama, & Murohashi, 2012).

1.8.5   Neural Correlates of Distracter Effects on Cognition

The neural mechanisms of filtering out task-irrelevant information and focusing on task-relevant information are complex. To summarize: the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) are two areas implemented in the cognitive control of attention. While the primary role of the DLPFC is to execute cognitive control by directing attention towards task-relevant stimuli, the role of the ACC is less clear but may involve conflict-monitoring (Egner & Hirsch, 2005; Kerns et al., 2004; Weissman, Warner, & Woldorff, 2004; Weissman, Giesbrecht, Song, Mangun, & Woldorff, 2003). It is postulated that in the presence of distracters (i.e. conflicts), the ACC signals the DLPFC to engage in top-down control that focuses attention on task-relevant stimuli. In order to process task-relevant information, the DLPFC has to recruit several other sensory regions that may be involved. However, there is also evidence showing that the role of the ACC may extend beyond conflict monitoring to executing top-down control along with the DLPFC. Using a cross-modal distraction paradigm, Weissman et al. (2005) demonstrated that parts of the ACC are involved in directing our attention towards task-relevant stimuli, similar to the DLPFC.

1.8.6   The Influence of Distracters on Cognition in MS

Despite extensive research on behavioral effects of distracters in the general population, there has been limited work involving distractions in the MS population or in the presence of brain damage for that matter. The effects of distracters on cognition amidst brain pathology could reveal unique effects not seen in healthy individuals. Research in MS has primarily utilized the Stroop paradigm to investigate distracter effects on cognition. However, the interference in the Stroop task is not equivalent to being distracted by auditory sounds. To better understand the

effects of distractions on cognitive functioning, it is important to review the nature of attention deficits in MS patients.

1.8.7 Attention in MS

Attention can be divided into different domains including sustained, selective and divided attention. Sustained attention or vigilance is the ability to focus on a particular task or stimulus over a long period of time. Selective attention involves focusing on specific stimuli, while ignoring other competing stimuli and divided attention allows us to multitask by focusing on two or more stimuli simultaneously.

Selective attention is one domain frequently impaired in MS. Slower performance of MS subjects on the Stroop task is commonly attributed to deficits in selective attention. The Stroop task was introduced by J. Ridley Stroop in 1935 and is considered a classic distracter task. MS subjects display significantly slower reaction times compared to healthy controls in completing a set of Stroop stimuli (Denney & Lynch, 2009; Macniven et al., 2008; Vitkovitch, Bishop, Dancey, & Richards, 2002). Whether impairment on the Stroop reflects a slowness in information processing speed, a deficit in selective attention, executive dysfunction or a combination of factors is open to debate.

Several studies utilizing different tests of attention have shown slower reaction times in MS subjects compared to controls. Deficits in divided attention using dual tasks have also been reported in the MS population, although there are exceptions where no significant deficits have been found (McCarthy, Beaumont, Thompson, & Peacock, 2005; Stoquart-El Sankari, Bottin, Roussel-Pieronne, & Godefroy, 2010; Tinnefeld et al., 2005; Urbanek et al., 2010). Despite the

40

use of different methods to assess selective, divided or sustained attention, a common finding amongst studies is slower reaction times in MS subjects compared to healthy controls, but no differences in response accuracy between the two groups. This suggest that people with MS sacrifice speed to maintain accuracy.

1.8.8 Auditory Distracters in MS

Researchers have utilized the auditory-oddball paradigm to assess electrophysiological effects of auditory distracters in MS. The results reveal faulty attention mechanisms in people with MS linked to general cognitive deficits. It has been shown via the two-stimulus oddball task that P3b latency (an event related potential (ERP) wave that measures the cognitive demands of a task) is increased significantly in people with MS and associated with slower information processing speed (Aminoff & Goodin, 2001; Ellger et al., 2002; Honig, Ramsay, & Sheremata, 1992; Kok, 2001). In addition to the P3b component, the MMN (an index of pre-conscious detection of unexpected sensory stimuli) and P3a (an index of attentional shift towards unexpected, deviant stimuli) have also been associated with cognitive impairments in MS (Jung, Morlet, Mercier, Confavreux, & Fischer, 2006). Overall, ERP studies demonstrate on a physiological level the attentional deficits that are prominent in MS subjects in response to auditory and/or visual distracter stimuli.

The study of distracters in MS has for the most part been confined to electrophysiological paradigms using auditory tones and deviant sounds administered in a testing room. The one exception is a study by LaPointe et al. (2005) of individuals with relapsing-remitting MS and healthy control subjects who were given different types of ecologically valid auditory distracters while performing visual cognitive tasks that included tests of simple and choice reaction time

and working memory. The auditory conditions included: 1) quiet 2) four-talker babble – four speakers reading a passage 3) word repetition – the examiner interrupted with words that the participant had to repeat and 4) combined four talker babble with word repetition. Reaction times were found to be significantly slower in MS subjects than in healthy controls for all the auditory conditions, but not in the quiet condition. Differences on cognitive tests within MS and control groups by auditory conditions was not reported. Of note is that the study sample only included individuals with mild disability, yet abnormalities were found, highlighting the sensitivity of this "real world" cognitive paradigm.

1.9 The Current Study

The traditional approach to neuropsychological testing involves the person with MS sitting with the psychometrician in an office free of distractions with a sign posted outside the door reading "do not disturb: testing in progress." Such an environment is often far removed from the commotion of real life and can help explain, in part, why some individuals who perform well in the stillness of a psychometricians office may fail to perform in the work place. A recent study has highlighted this point by showing that heightened distractibility in people with MS who are deemed cognitively intact on the MACFIMS is associated with deficits in attention and working memory (Feinstein, Lapshin, & O'Connor, 2012). This is of particular significance in MS, since subtle cognitive deficits, which often go undetected are known to be present early in the disease. The incorporation of distracters into conventional neuropsychological tests may therefore help reconcile differences between the testing and real world environments thereby bridging the ecological divide.

There is also another incentive for exploring the use of distracters in neuropsychological testing. As mentioned earlier, cognitive reserve is known to be protective of cerebral compromise in individuals with Alzheimer's disease, stroke and multiple sclerosis. Thus, individuals with a high cognitive reserve may perform within the normal range on conventional cognitive testing, but fail to function at a level commensurate to their innate abilities in their high end, intellectually demanding jobs. Here distracters may offer new insights by challenging individuals in a way that unmasks a more complete picture of their cognitive failings.

The effects of auditory distracters on cognitive functioning is limited to a single study in the MS population (LaPointe et al., 2005). This study, while informative, had number of limitations. These included a small sample size (22 MS subjects and 17 healthy controls), subjects with only relapsing-remitting disease and mild disability, and the administration of cognitive tests not typically used in people with MS.

Aims:

Three primary factors determined the aim of the present study:

1) The dearth of literature relating to the use of auditory distracters in people with MS

2) The potential utility of distracters in testing cognition in people with MS

3) The known sensitivity of the SDMT in detecting cognitive dysfunction in MS

The aim of the study was therefore to develop and validate a computerized, auditory distracter version of the SDMT. The decision to develop a computerized version was dictated by the need to standardize and facilitate presentation.

Hypotheses:

1) Subjects will perform slower on the computerized distracter version of the SDMT than the non-distracter version, with differences being more prominent in MS subjects

2) The computerized distracter SDMT is more sensitive in detecting cognitive dysfunction than the computerized non-distracter and the conventional paper version of the test

3) The computerized distracter SDMT will detect greater deficits in people with high cognitive reserve than traditional neuropsychological testing

CHAPTER 2: METHODS

2.1 Sample Selection

2.1.1 MS Subjects

Individuals with a confirmed diagnosis of MS based on the modified McDonald criteria (Polman et al., 2011) were recruited through two outpatient MS clinics. Subjects with relapsing remitting MS (RRMS), secondary progressive MS (SPMS) or primary progressive MS (PPMS) between the ages of 18 to 65 were enrolled. Subjects older than 65 years of age were excluded to mitigate the effects of age-related cognitive decline. Subjects were also excluded if they had a history of another disease of the central nervous system other than MS, traumatic brain injury, psychosis, learning disability, history of substance abuse, previous neuropsychological testing done within the past year, or visual acuity less than 20/70, the latter in accordance with standard neuropsychological testing protocol.

2.1.2 Healthy Controls

Healthy controls (HC) between the ages of 18 to 65 were also enrolled. The exclusion criteria for HC subjects were the same as those for MS subjects.

2.2 Subject Recruitment

The study took place at two sites, the Sunnybrook Health Sciences Centre in Toronto and the Ottawa General Hospital. MS subjects were recruited by a research assistant from outpatient MS clinics at both sites. HC subjects were recruited via study flyers posted throughout the

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www.manaraa.com

hospital bulletin boards. In addition, family members accompanying MS subjects during their study visit were informed about the study and asked to participate as a healthy volunteer.

All subjects were reimbursed for parking and transportation costs after their study visit. Results of the cognitive testing were also made available upon request.

2.2.1   MS Research Portal

Research advertisements for both MS and HC subjects were posted on the MS Research Portal, a website maintained by the Multiple Sclerosis Society of Canada that informs individuals about ongoing MS research studies. Interested individuals were requested to contact the research assistant via email or telephone.

2.3   Ethics

This study received ethics approval from the Research Ethics Boards at Sunnybrook Health Sciences Centre and The Ottawa Hospital – General Campus. Informed consent was obtained from all subjects.

2.4   Data Collection Measures

2.4.1   Demographic Data

Demographic variables included age, sex, years of education, marital status, and employment status. The demographic questionnaire was administered to all subjects prior to cognitive testing.

2.4.2   Disease Related Data

Disease related variables included disease course, illness duration, medication history, history of psychiatric illness (depression, anxiety, bipolar disorder, etc...), and level of physical disability

based on the Expanded Disability Status Scale (EDSS). Disease course, medication and psychiatric history data were collected from medical charts and EDSS scores were obtained from the attending neurologist. Visual acuity and colour blindness were also assessed using the Snellen near vision eye chart prior to cognitive testing.

2.4.3 Cognitive Assessment

a. Computerized Symbol Digit Modalities Test with and without built-in distracters

The computerized Symbol Digit Modalities Test (c-SDMT) is a version of the standard SDMT that measures information processing speed. An earlier version without distracters has previously been validated for use in MS (Akbar, Honarmand, Kou, et al., 2011). In the c-SDMT, a row of 9 boxes each filled with a symbol is presented on the computer screen. Above the row of boxes is a key that matches each symbol with a number 1 to 9. Using the key, the subject is instructed to verbally match each symbol with a number, starting from the far left symbol and proceeding to the right, as quickly as possible. Before starting the test, a practice trail is given to ensure proper understanding. The test consists of eight trials in total. As soon as the subject matches the last symbol with a number for a given trial, the administrator clicks the mouse and the bottom row of boxes fills with a new set of symbols in a different order from the previous trial. The key however remains fixed. Figure 1 displays a screen shot of the c-SDMT. The time to complete each trial (in seconds) is automatically recorded by the computer. In addition, the computer generates a total time and a mean overall time for the eight trials. The administrator records the number of errors made for each trial.

47

The c-SDMT was modified by inserting real-world distracters into the test. In trial two of the test, a telephone rings, in trial five a car horn goes off and in trial 7 a telephone rings again. These sounds were chosen as they simulate real-world intrusions. As this is a novel approach to cognitive testing and there are no precedents, we decided to include distracters in only 3 of the 8 trials. Each distracter lasted for 8 seconds and was played through an external speaker system attached to the computer. Distracters were presented at a loudness of 100 decibels. Failure on the c-SDMT was defined as a score greater than 1.5 standard deviation (SD) above the normative mean derived from HC subjects.

Figure 1: Screenshot of the c-SDMT
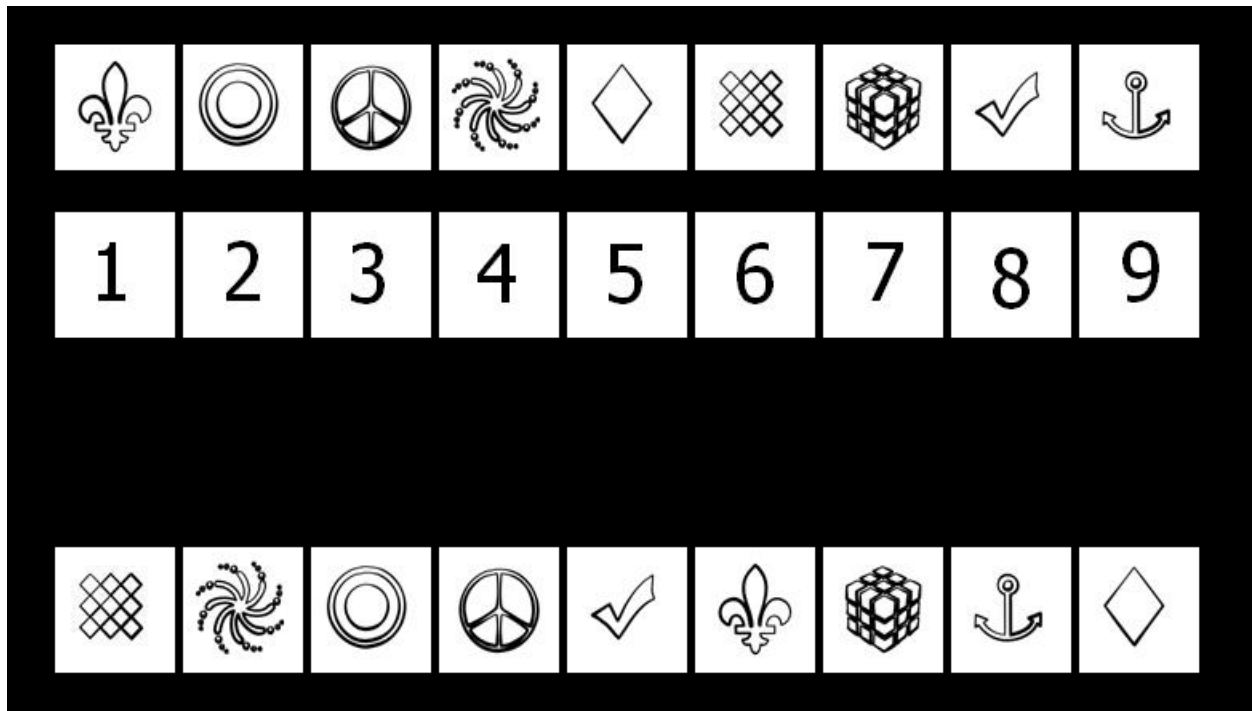
b. The Minimal Assessment of Cognitive Functioning in Multiple Sclerosis (MACFIMS)

The MACFIMS is an expert consensus derived battery of tests, sensitive to cognitive impairment in MS (Benedict et al., 2002). The battery takes 90-minutes to administer and consists of seven tests measuring five cognitive domains: 1) information processing speed, 2) verbal and visual learning and memory, 3) executive functioning, 4) visuospatial processing and 5) verbal fluency. Normative data have been published for each test, however, for scoring purposes normative data obtained from a sample of HC subjects who completed the MACFIMS were used (n=51).

i. *Information Processing Speed*

Paced Auditory Serial Addition Test (PASAT)

The PASAT is a measure of information processing speed as well as working memory (Gronwall, 1977). In the test, subjects listen to an audio tape that presents a series of sixty numbers between 1 and 9. In the first trial, the numbers are presented at every 3 seconds (PASAT-3) and in the second trial at every 2 seconds (PASAT-2). Subjects were instructed to verbally add each consecutive number to the one immediately preceding it (e.g. if the numbers "3, 5, 7" are presented, subjects would have to respond "8, 12"). Since the audio tape would not be stopped once the test was started, subjects were informed beforehand that if they fell behind in responding, they can jump back into the test by listening to the next two consecutive numbers. A brief practice trial was conducted before beginning the actual test. The raw score on the test is the total number of correct responses in each of the two trials.

Symbol Digit Modalities Test (SDMT)

The pencil and paper SDMT is a sensitive measure of information processing speed (Smith, 1982). In the test, subjects are presented with an 8.5 x 11 in. paper that contains a key at the top of the page comprised of 9 different symbols matched with numbers 1 to 9. The rest of the page contains consecutive rows of boxes containing symbols in a random order. Subjects were instructed to verbally match each symbol with a number as quickly and accurately as possible using the key at the top. A practice trial was conducted before administering the test. The raw score is the number of correct responses given in 90-seconds.

ii. **Verbal and Visual Learning & Memory**

California Verbal Learning Test – II (CVLT-II)

The CVLT-II is a measure of verbal learning and memory (Delis, Kramer, Kaplan, & Ober, 2000). The first part of the test was the immediate free recall, in which subjects were read a list of 16 words from four categories (animals, modes of transportation, vegetables and furniture) and asked to recall the items in any order. The words were presented in a random order, at the rate of 1 word per second. After recall, the same list was read again and this was repeated for a total of 5 trials. The first primary measure of the test is the total number of words recalled on the 5 trials. Next came the interference trial, in which subjects were read a second list of 16 words and asked to recall the items in any order. After the interference trial, short-delay free recall was assessed by asking subjects to recall items only from the first list of words that was read to them 5 times. Then, short delay cued recall was assessed by asking subjects to recall the words from

51

the first list belonging to a specific category (e.g. "list the words that were modes of transportation").

The second part of the CVLT-II was completed after a 20-minute interval. A long-delay free recall trial was conducted, in which subjects were asked to list the words they remember from the first list that was read to them 5 times. The second primary measure of the test is the total number of words recalled on the long-delay free recall. Following this was the long-delay cued recall and the recognition trial. In the recognition trial, subjects were read a list of 32 words (in which 16 belonged to the first list and 16 were distracter words) and after each word they were asked to respond "yes" if the word was from the first list and "no" if it was not.

Brief Visuospatial Memory Test – Revised (BVMT-R)

The BVMT-R is a test of visual learning and memory (Benedict, 1997). In the first part, subjects were shown a display of six figures on a sheet of 8.5 x 11 in. paper for 10 seconds and asked to study the figures. After 10 seconds, the display was taken away and subjects were asked to draw the six figures as accurately as possible and in the correct location on the page. This was repeated for a total of three trails using the same set of figures. The first primary measure of the test is the total points scored on the three trials for immediate recall. For scoring, the BVMT-R professional manual was used where 1 point is given for drawing the correct figure and 1 point for location. After the three immediate recall trials, subjects were told to keep the figures in memory as best as possible because they will be asked later in the testing process to draw them again.

Following a 20-minute interval, subjects were asked to draw the six figures again to assess delayed memory. The second primary measure of the test is the total points scored on the delayed memory trial. The same scoring procedure was used as the immediate recall trials. After assessing delayed memory, a recognition trial was conducted in which subjects were shown 12 figures in a booklet (6 targets and 6 distracters) and asked to respond "yes" if the figure presented was one of the six viewed earlier.

In addition to the two primary measures, secondary measures were also collected which included BVMT-R learning score, percentage of information retained in delayed memory and number of hits and false alarms on the recognition trial. The learning score was calculated by subtracting the raw score of trial 1 from the higher score of either trial 2 or 3 in immediate recall. Percentage of information retained was calculated using the following formula: (delayed recall score/highest score of immediate recall) x 100.

iii. *Executive Functioning*

Delis-Kaplan Executive Function System (D-KEFS) Sorting Test

The D-KEFS sorting test is a task that evaluates components of executive functioning (Delis, Kaplan, & Kramer, 2001). Subjects were presented with a set of 6 cards, each having a word written in the center and containing several different perceptual features (e.g. shape, colour). For the test, subjects were asked to form two groups, with three cards in each group such that all the cards in one group have a common feature associated with them. Sorts can be made based on verbal features using the words on the cards or perceptual features. Subjects were also asked to give a clear description for

their sort. Two trials using different sets of cards were conducted. Administration of a trial was discontinued once the subject stated they cannot form any more sorts, a cumulative time of four minutes had passed or the subject had attempted 10 total sorts for the trial. The examiner recorded the sorts and the corresponding descriptions. A previously developed manual was used for scoring and primary measures included the total number of correct sorts and the total description score for the two trials.

iv. *Visuospatial Orientation*

Judgement of Line Orientation (JLO)

The JLO is a test that assess visuospatial processing (Benton, Sivan, Hamsher, Varney, & Spreen, 1994). In a testing booklet, a key was presented with an arrangement of eleven lines from 0 to 180 degrees, each with a number 1 to 11 associated with it. Above it, two stimuli lines were presented, each in a different orientation that corresponded to one of the lines in the key. Subjects were instructed to use the key and verbally match the two stimuli lines with their associated numbers. A practice trial of 5 stimuli was conducted before starting the test stimuli. The primary measure is the total number of correct responses out of 30.

v. *Verbal Fluency*

Controlled Oral Word Association Test (COWAT)

The COWAT is a test of phonemic fluency (Benton & Hamsher, 1989). In the test, subjects were given 1 minute to generate as many words as possible that began with a particular letter of the alphabet. Subjects were instructed to refrain from using proper nouns (e.g. people name such as "Bob" or places like "Europe"), counting numbers (e.g.

54

fifty-one, fifty-two, fifty-three, etc...) and using similar words with different a suffix (e.g. if the subject said the word "eat" they cannot respond again with "eating" or "eaten"). The test is not a measure of pure language proficiency as performance is influenced by efficiency and speed of retrieving words from one's vocabulary. A total of three trials was conducted with the letters F, A and S. The primary outcome is the total number of words generated in the three trials. After the FAS trial, subjects were asked to name as many different kinds of animals as they can, irrespective of what letter they began with. The secondary outcome is the total number of animals named in one minute.

Global Cognitive Impairment on the MACFIMS

Failure on each cognitive index was defined as a score of 1.5 SD below mean normative scores obtained from healthy controls matched for age, gender, education and premorbid IQ. Conventionally, global impairment on the MACFIMS is defined as impairment on 2 or more of the 11 cognitive indices. However, global impairment in this study was defined as failure on three or more cognitive indices (see results for rationale).

2.4.4 Depression and Anxiety

Depression and anxiety were assessed in both MS and HC subjects using the 14-item Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). The HADS scale measures self-reported mood within one week prior to cognitive testing and it has been previously validated for use in the MS population (Honarmand & Feinstein, 2009). Additionally, it excludes confounding effects of vegetative symptoms (e.g. fatigue and sleep disturbances) that are common in both depression and MS. The scale consists of 7 items for depression and 7 for

anxiety. Each item was scored using a four point scale ranging from 0 to 3. The total score on each subscale ranges from 0 – 21, with a score of 8 or higher used as an indication for clinically significant depression and anxiety.

2.4.5 Fatigue

The modified Fatigue Impact Scale (m-FIS) is a 21-item self-report measure that assess the impact of fatigue on everyday life. The m-FIS is a shorter version of the 40-item Fatigue Impact Scale and has been previously validated for use in MS (Fisk et al., 1994). Of the 21 items, 9 assess fatigue in the physical domain, 10 in the cognitive domain and 2 in the psychosocial domain. Subjects were asked to indicate the impact fatigue has had on their life in the last 4 weeks using a scale that ranged from 0 to 4 (0: no problem, 1: small problem, 2: moderate problem, 3: big problem, and 4: extreme problem). The total scores range from 0 to 84, with higher scores indicative of greater fatigue on a daily basis.

2.4.6 Cognitive Reserve

a. Wechsler Test of Adult Reading (WTAR)

Premorbid intelligence was used as a proxy for cognitive reserve. Premorbid IQ was estimated based on verbal vocabulary knowledge, which was assessed using the Wechsler Test of Adult Reading (WTAR, Holdnack, 2001). On a word card, subjects were presented with a list of 50 words, with irregular spellings, and asked to pronounce each word. Each correct pronunciation was awarded 1 point, with a maximum achievable score of 50. Using published norms, the raw WTAR score was converted into a standard score, which was then used to obtain an estimated Full Scale IQ (FSIQ) on the Wechsler Adult Intelligence Scale – third edition (WAIS-III; Wechsler, 1997). For analysis, subjects

56

were categorized into either high or average/low cognitive reserve groups based on the WAIS-III IQ classifications ($\geq$ 69: extremely low, 70-79: borderline, 80-89: low average, 90-109: average, 110-119: high average, 120-129: superior, and $\geq$ 130: very superior). Subjects with a premorbid IQ of $\geq$ 110 were grouped as having high cognitive reserve and those below 110 as having average/low cognitive reserve. The average and low cognitive reserve groups were combined for analysis because only 7 MS subjects were classified as having a low cognitive reserve (IQ below 90).

b. **Leisure Activity Scale (LAS)**

The leisure activity scale (LAS) was used to determine the degree to which subjects pursued non-work related leisure activities (J F Sumowski et al., 2010). The LAS was recently developed to assess the influence of premorbid cognitive leisure on cognitive functioning in MS, but the scale has also been extended to assess social and physical leisure activity pursuit. The LAS is a 20-item self-report measure that consists of 8 items assessing the frequency of cognitive leisure, 5 for social leisure and 7 assessing physical leisure. Subjects used a rating scale from 1 to 5 (1: daily, 2: several times per week, 3: several times per month, 4: several times per year and 5: once/less per year) to indicate their frequency of participation for each activity. The total scores range from 0 to 100, with higher scores indicating greater level of leisure activity pursuit. In this study, subjects were asked to retrospectively report their level of leisure activity in their early 20s, early 30s and in the most recent year.

2.5 Testing Procedures

The order of test administration was as follows:

1) Informed consent
2) Interview to obtain demographic data
3) Visual acuity test with Snellen eye chart
4) c-SDMT (with or without distracters)
5) BVMT-R – Immediate recall trials
6) WTAR
7) PASAT (3 and 2 second versions)
8) COWAT (FAS and Animal trial)
9) BVMT-R – Delayed recall trial
10) CVLT-II – Immediate recall trials, short delayed free recall and short delayed cued recall
11) Traditional SDMT
12) D-KEFS sorting test
13) JOLO
14) CVLT-II – Delayed recall trial
15) HADS
16) M-FIS
17) LAS

All consecutive odd numbered subjects completed the c-SDMT with distracters and consecutive even numbered subjects without. The c-SDMT (with or without distracters) was administered first as this was the novel approach under investigation and to avoid any practise effects from the traditional SDMT that is part of the MACFIMS. Furthermore, the c-SDMT takes only 5 minutes to complete, compared to the 90-minute MACFIMS. Therefore to limit the influence of fatigue the c-SDMT was administered first. The MACFIMS battery was given to all MS subjects, but only in a subset of HC subjects due to their time constraints. All HC subjects completed the c-SDMT and self-report questionnaires (HADS, M-FIS, and LAS).

Three months after initial baseline testing, every third person with MS (n=26) and every third control subject (n=17) was selected for retesting on the c-SDMT with or without distracters depending on the initial condition they received. In addition, the self-report measures of

depression, anxiety and fatigue were repeated. None of the MS subjects experienced a disease relapse or change in neurological status since initial baseline testing.

2.6   Statistical Analysis

The Kolmogorov-Smirnov test was used to determine if demographic, neurologic, psychiatric and cognitive data were normally distributed. A Student's t-test was used to compare normally distributed data and a Mann-Whitney U test for non-normally distributed data. Ordinal data were compared using chi-squared (x^2) analyses.

A repeated measures ANOVA was used to test within and between subject effects on the c-SDMT. MS and HC subjects were divided into those who received the distracter versus non-distracter c-SDMT. Within each task comparisons were undertaken between MS and HC groups. Within MS and HC subjects, comparisons were also made between distracter versus non-distracter task.

Sensitivity and specificity calculations were conducted for the three versions of the SDMT (distracter and non-distracter c-SDMT and traditional SDMT) in detecting global cognitive impairment relative to the MACFIMS. On the MACFIMS failure on 3 or more cognitive indices served as the 'gold standard' for global cognitive impairment. Receiver operating characteristic (ROC) analysis was also undertaken to determine the discriminative value of each test.

Test-retest reliability of the c-SDMT with and without distracters was ascertained using an intra-correlation coefficient, two-way fixed model.

Cognitive reserve analysis:

Cognitive data were compared between those with high versus average/low cognitive reserve. High cognitive reserve was defined as a premorbid IQ greater than or equal to 110. Level of leisure activity pursuit data during discreet age periods (20s, 30s and most recent year) were also compared between subjects cognitively intact versus impaired on the MACFIMS and the c-SDMT with distracters.

Influence of anxiety and depression:

The influence of anxiety and depression on the effects of distracters was assessed using the HADS. A cut-off score of 8 or higher on the two subscales was used as an indication for clinically significant depression and anxiety. Cognitive comparisons were made between MS subjects depressed and non-depressed, and anxious and non-anxious. A linear regression analysis was conducted to determine if depression, anxiety or both predicted performance on the c-SDMT with and without distracters.

CHAPTER 3: RESULTS

3.1   Sample Demographics and Disease Related Data

A total of 103 MS and 69 HC subjects were recruited. One MS subject was excluded from analysis due to a diagnosis of Clinically Isolated Syndrome. The final sample for analysis therefore included 102 MS and 69 HC subjects. Demographic comparisons between MS and HC subjects and neurologic data are displayed in Table 1. Data are split into distracter and non-distracter groups. There were no differences with respect to age, gender, and years of education between MS and HC subjects in both distracter and non-distracter conditions. Comparisons between MS subjects in the distracter versus non-distracter groups on demographic, neurologic and psychiatric variables are presented in Table 2. There were no differences, with the exception of the distracter group having higher anxiety scores.

3.2   Cognitive Data

3.2.1 Minimal Assessment of Cognitive Functioning in MS (MACFIMS)

Comparisons between MS subjects and healthy controls on the MACFIMS battery are shown in Table 3. Significant differences between MS and HC subjects were found for all cognitive indices, with the exception of visuospatial processing (Judgement of Line Orientation test) and one measure of executive function (D-KEFS total description). Conventionally, global impairment is defined as impairment on 2 or more cognitive indices on the MACFIMS. However, 15 (14.7%) subjects were not able to complete the faster 2 second version of the PASAT due to its difficulty. Furthermore, 6 MS subjects failed only the 3 and 2 second PASAT and no other cognitive test. To avoid defining global impairment based on dysfunction on a single cognitive task (e.g. information processing speed grounded on only two PASAT scores) the criteria was

modified to failure on 3 or more cognitive indices. With this criteria 39 (38.2%) MS subjects were found to be globally impaired. There were no differences in disease course or illness duration between MS subjects cognitively impaired versus intact, however, impaired subjects had a significantly greater age (47.79 vs. 42.65, p=0.011, respectively) and higher EDSS scores (3.28 vs. 2.33, p=0.02, respectively).

Table 1: Demographics and disease characteristics of MS and HC subjects

	Distracter Trials			
	MS subjects – mean (SD) /frequency (%); n = 52	HC subjects – mean (SD) /frequency (%); n = 36	t-test/x^2	p-value
Age (Years)	45.00 (10.09)	41.28 (14.30)	t = -1.433	p = 0.156
Sex (% female)	39 (75.0%)	22 (61.1%)	x^2 = 1.929	p = 0.165
Years of Education	14.96 (1.76)	15.11 (2.00)	t = 0.371	p = 0.712
Illness Duration (Years)	11.51 (9.02)			
EDSS	2.74 (2.12)			
Disease Course				
RRMS	35 (67.3%)			
SPMS	14 (26.9%)			
PPMS	3 (5.8%)			
	Non-Distracter Trials			
	MS subjects – mean (SD) /frequency (%); n = 50	HC subjects – mean (SD) /frequency (%); n = 33	t-test/x^2	p-value
Age (Years)	44.20 (10.02)	41.42 (13.03)	t = -1.094	p = 0.277
Sex (% female)	31 (62.0%)	22 (66.7%)	x^2 = 0.188	p = 0.665
Years of Education	14.66 (2.61)	15.70 (2.35)	t = 1.842	p = 0.069
Illness Duration (Years)	10.54 (7.38)			
EDSS	2.64 (1.94)			
Disease Course				
RRMS	36 (72.0%)			
SPMS	9 (18.0%)			
PPMS	5 (10.0%)			

Abbreviations: RRMS – Relapsing Remitting Multiple Sclerosis; SPMS – Secondary Progressive Multiple Sclerosis; PPMS – Primary Progressive Multiple Sclerosis; EDSS – Expanded Disability Status Scale

Table 2: Comparison of demographic, neurologic and psychiatric data between MS subjects in the distracter and non-distracter groups

	MS distracter – mean (SD) /frequency (%); n = 52	MS non-distracter – mean (SD) /frequency (%); n = 50	t-test/x^2	p-value
Age (years)	45.00 (10.09)	44.20 (10.02)	t=0.402	p=0.689
Sex (% female)	39 (75.0%)	31 (62.0%)	x^2=2.001	p=0.157
Years of education	14.96 (1.76)	14.66 (2.61)	t=0.682	p=0.497
Illness duration (years)	11.51 (9.02)	10.54 (7.38)	t=0.591	p=0.556
EDSS	2.74 (2.12)	2.64 (1.94)	t=0.287	p=0.804
% of disease modifying medication	29 (55.8%)	33 (66.0%)	x^2=1.119	p=0.290
Disease course				
RRMS	35 (67.3%)	36 (72.0%)	x^2=0.265	p=0.607
SPMS	14 (26.9%)	9 (18.0%)	x^2=1.162	p=0.281
PPMS	3 (5.8%)	5 (10.0%)	x^2=0.631	p=0.427
M-FIS fatigue	41.20 (19.66)	39.04 (15.07)	t=0.618	p=0.538
HADS anxiety	8.46 (3.90)	6.72 (4.10)	t=2.197	p=0.030
HADS depression	5.92 (3.93)	5.04 (3.59)	t=1.184	p=0.239

Abbreviations: EDSS – Expanded Disability Status Scale; RRMS – Relapsing Remitting Multiple Sclerosis; SPMS – Secondary Progressive Multiple Sclerosis; PPMS – Primary Progressive Multiple Sclerosis; M-FIS – Modified Fatigue Impact Scale; HADS – Hospital Anxiety and Depression Scale; PSQI – Pittsburgh Sleep Quality Index

Table 3: Comparison of cognitive data on the MACFIMS and psychiatric data between MS and HC subjects

	MS subjects – mean (SD) n = 102	HC subjects – mean (SD) n = 53	t-test	p-value
BVMT-R total	20.63 (7.89)	25.51 (7.40)	t=3.732	p<0.001
BVMT-R delayed recall	8.22 (3.13)	10.34 (1.99)	t=4.492	p<0.001
CVLT-II total	49.47 (12.06)	57.32 (8.12)	t=4.804	p<0.001
CVLT-II delayed recall	10.43 (3.88)	12.77 (2.52)	t=4.533	p<0.001
PASAT – 2 second	30.54 (11.05)	34.25 (9.65)	t=2.077	p=0.040
PASAT – 3 second	40.19 (13.54)	46.62 (10.17)	t=3.256	P=0.001
SDMT	46.88 (13.20)	57.88 (10.41)	t=5.236	p<0.001
D-KEFS sorting	9.44 (2.54)	10.38 (2.26)	t=2.268	p=0.025
D-KEFS description	34.19 (9.59)	37.09 (9.65)	t=1.783	p=0.077
COWAT	35.62 (11.38)	41.34 (11.08)	t=2.996	p=0.003
JLO	25.43 (4.01)	25.42 (3.86)	t=-0.016	p=0.987
M-FIS fatigue	40.13 (17.48)	19.22 (15.04)	t=-8.055	p<0.001
HADS anxiety	7.61 (4.08)	5.62 (3.66)	t=-3.246	p=0.001
HADS depression	5.49 (3.77)	2.37 (2.42)	t=-6.569	p<0.001

Abbreviations: BVMT-R – Brief Visuospatial Memory Test- Revised; CVLT-II – California Verbal Learning Test, second edition; PASAT – Paced Auditory Serial Addition Test; SDMT – Symbol Digit Modalities Test; D-KEFS – Delis-Kaplan Executive Function System; COWAT – Controlled Oral Word Association Test; JLO – Judgement of Line Orientation Test; M-FIS – Modified Fatigue Impact Scale; HADS – Hospital Anxiety and Depression Scale; PSQI – Pittsburgh Sleep Quality Index

3.2.2 Computerized Symbol Digit Modalities Test (c-SDMT) – With and Without Built-in Distracters

A mixed ANOVA model was used to test within and between subject effects on the c-SDMT (Table 4). A full factorial model with main effects and all possible interactions between group (MS vs. HC), task (distracter vs. non-distracter) and time (across 8 trials of the test) was conducted first. A second model was also assessed after removing non-significant interactions. The mean time (seconds) on the 8 trials of the c-SDMT was significantly higher in MS than HC subjects for both distracter (18.10 [SD: 10.31] vs. 12.77 [SD: 2.26]; z=-3.849, p<0.001) and non-distracter (15.92 [SD: 5.63] vs. 12.14 [SD: 1.73]; z=-4.438; p<0.001) version. There was a significant group x time interaction on both the distracter and non-distracter c-SDMT suggesting that changes in speed across trials were not consistent between groups.

Subjects were slower on the distracter task than the non-distracter, but within group differences were not significant (MS: z=-0.803, p=0.422 and HC: t=1.276, p=0.207). Moderate effect sizes were found for c-SDMT trials that contained distracters (Table 5). A significant task x time interaction was found within MS (p=0.019), but not HC subjects.

There were no differences in response accuracy between the distracter and non-distracter c-SDMT for either MS (mean error rate: 1.17 vs. 1.12 respectively, z=-0.383, p=0.702) or HC (0.58 vs. 0.42 respectively, z=-0.722, p=0.470) subjects.

66

Table 4: Within and between subject effects on the computerized SDMT

	Model 1: Full factorial	
	F	**p-value**
Group (MS vs. HC)	F=33.059	p<0.001
Task (distracter vs. non-distracter)	F=1.972	p=0.162
Time	F=65.718	p<0.001
Group x Task	F=0.183	p=0.669
Group x Time	F=2.973	P=0.007
Task x Time	F=2.120	p=0.048
Group x Task x Time	F=1.630	p=0.134
	Model 2*	
	F	**p-value**
Group (MS vs. HC)	F=33.427	p<0.001
Task (distracter vs. non-distracter)	F=2.309	p=0.130
Time	F=65.546	p<0.001
Group x Time	F=2.936	p=0.007
Task x Time	F=2.481	p=0.021
*Non-significant interaction terms from Model 1 were removed		

67

Table 5: Mean time on c-SDMT across 8 trials within MS and HC subjects

	MS Subjects				
	Distracter – mean (SD); n = 52	Non-distracter – mean (SD); n = 50	z	p-value	Effect size (r)
Trial 1	18.66 (10.33)	17.38 (6.41)	z=-0.689	p=0.491	r=0.07
Trial 2*	19.87 (10.11)	17.00 (6.54)	z=-1.633	p=0.102	r=0.17
Trial 3	18.95 (12.86)	17.13 (7.24)	z<0.001	p=0.999	r=0.09
Trial 4	17.65 (8.61)	15.93 (5.58)	z=-0.910	p=0.363	r=0.12
Trial 5*	17.78 (10.16)	15.69 (6.49)	z=-0.924	p=0.356	r=0.12
Trial 6	16.89 (9.74)	14.60 (4.79)	z=-0.522	p=0.602	r=0.15
Trial 7*	17.13 (11.51)	13.75 (6.21)	z=-1.948	p=0.051	r=0.18
Trial 8	17.86 (11.41)	15.91 (6.03)	z=-0.114	p=0.909	r=0.11
Mean Time	18.10 (10.31)	15.92 (5.63)	z=-0.803	p=0.422	r=0.13
	HC subjects				
	Distracter – mean (SD); n = 36	Non-distracter – mean (SD); n = 33	t-test	p-value	Cohen's d
Trial 1	13.47 (3.21)	12.85 (1.99)	t=0.952	p=0.344	d=0.23
Trial 2*	13.88 (2.30)	13.63 (2.19)	t=0.454	p=0.651	d=0.11
Trial 3	13.62 (2.82)	12.72 (2.22)	t=1.471	p=0.146	d=0.35
Trial 4	12.78 (2.85)	12.25 (2.13)	t=0.864	p=0.390	d=0.21
Trial 5*	11.88 (1.99)	11.06 (1.67)	t=1.843	p=0.070	d=0.45
Trial 6	12.53 (2.67)	11.62 (2.14)	t=1.545	p=0.127	d=0.38
Trial 7*	11.28 (2.27)	10.57 (1.76)	t=1.442	p=0.154	d=0.35
Trial 8	12.69 (2.43)	12.93 (2.79)	t=-0.371	p=0.712	d=0.09
Mean Time	12.77 (2.26)	12.14 (1.73)	t=1.276	p=0.207	d=0.31

*Trials with distracters presented

68

3.2.3 Impairment Rates on Three Versions of the SDMT

The percentage of MS subjects impaired on the traditional SDMT, the c-SDMT with distracters and c-SDMT without distracters were 29.4%, 36% and 46.2% (x^2=4.242, p=0.12). Significantly more subjects were impaired on the c-SDMT with distracters than the traditional SDMT (x^2=4.240, p=0.039), but there were no differences between the c-SDMT without distracters and the traditional SDMT (x^2=0.674, p=0.412). There were also no differences in impairment rates between the c-SDMT with distracters versus without (x^2=1.085, p=0.298).

By disease course, significantly more people with progressive MS were impaired compared to RRMS on both the c-SDMT with distracters (76.5% vs. 31.4%, x^2=10.152, p=0.006) and without distracters (64.3% vs. 25%, x^2=7.586, p=0.023).

3.2.4 Sensitivity and Specificity Analysis

The sensitivity and specificity of the traditional SDMT, the c-SDMT with and without distracters in detecting global cognitive impairment relative to the MACFIMS is shown in Table 5. Using a conventional 1.5SD cut-off, the c-SDMT with distracters had higher sensitivity (81.8%) in detecting global impairment than both the c-SDMT without distracters (70.6%) and the traditional SDMT (64.1%). The high sensitivity of the distracter task, however, was offset by a lower specificity than the traditional SDMT. The positive and negative predictive values for the distracter c-SDMT were 75% and 86% respectively. The values for the non-distracter test were 67% and 84% and for the traditional SDMT 83% and 81% respectively.

A ROC analysis for the traditional SDMT and the c-SDMT with and without distracters revealed

an area under the curve (AUC) of 0.893 (p<0.001), 0.882 (p<0.001) and 0.836 (p<0.001),

respectively (Figures 2-4).

Table 6: Sensitivity and specificity table of the three versions of the SDMT in detecting global cognitive impairment relative to the MACFIMS

Standard deviation cut-off	Distracter c-SDMT		Non-distracter c-SDMT		Traditional SDMT	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
0.50	**95.5%**	**53.3%**	**94.1%**	**36.4%**	**92.3%**	**52.4%**
0.60	95.5%	56.7%	94.1%	39.4%	92.3%	54.0%
0.70	95.5%	63.3%	88.2%	42.4%	92.3%	58.7%
0.80	95.5%	66.7%	88.2%	45.5%	89.7%	66.7%
0.90	95.5%	73.3%	88.2%	48.5%	89.7%	71.4%
1.00	**90.9%**	**73.3%**	**88.2%**	**51.5%**	**87.2%**	**71.4%**
1.10	90.9%	76.7%	88.2%	54.5%	84.6%	74.6%
1.20	90.9%	80.0%	82.4%	63.6%	82.1%	77.8%
1.30	86.4%	80.0%	82.4%	66.7%	79.5%	81.0%
1.40	81.8%	80.0%	82.4%	69.7%	79.5%	87.3%
1.50	**81.8%**	**80.0%**	**70.6%**	**81.8%**	**64.1%**	**92.1%**
1.60	81.8%	80.0%	70.6%	81.8%	59.0%	93.7%
1.70	81.8%	83.3%	70.6%	84.8%	59.0%	93.7%
1.80	77.3%	86.7%	70.6%	84.8%	56.4%	95.2%
1.90	68.2%	86.7%	70.6%	84.8%	56.4%	96.8%
2.00	**63.6%**	**86.7%**	**70.6%**	**84.8%**	**48.7%**	**96.8%**

c-SDMT: computerized Symbol Digit Modalities Test; MACFIMS: Minimal Assessment of Cognitive Functioning in Multiple Sclerosis

71

Figure 2: ROC curve for the traditional SDMT in detecting cognitive impairment relative to the MACFIMS
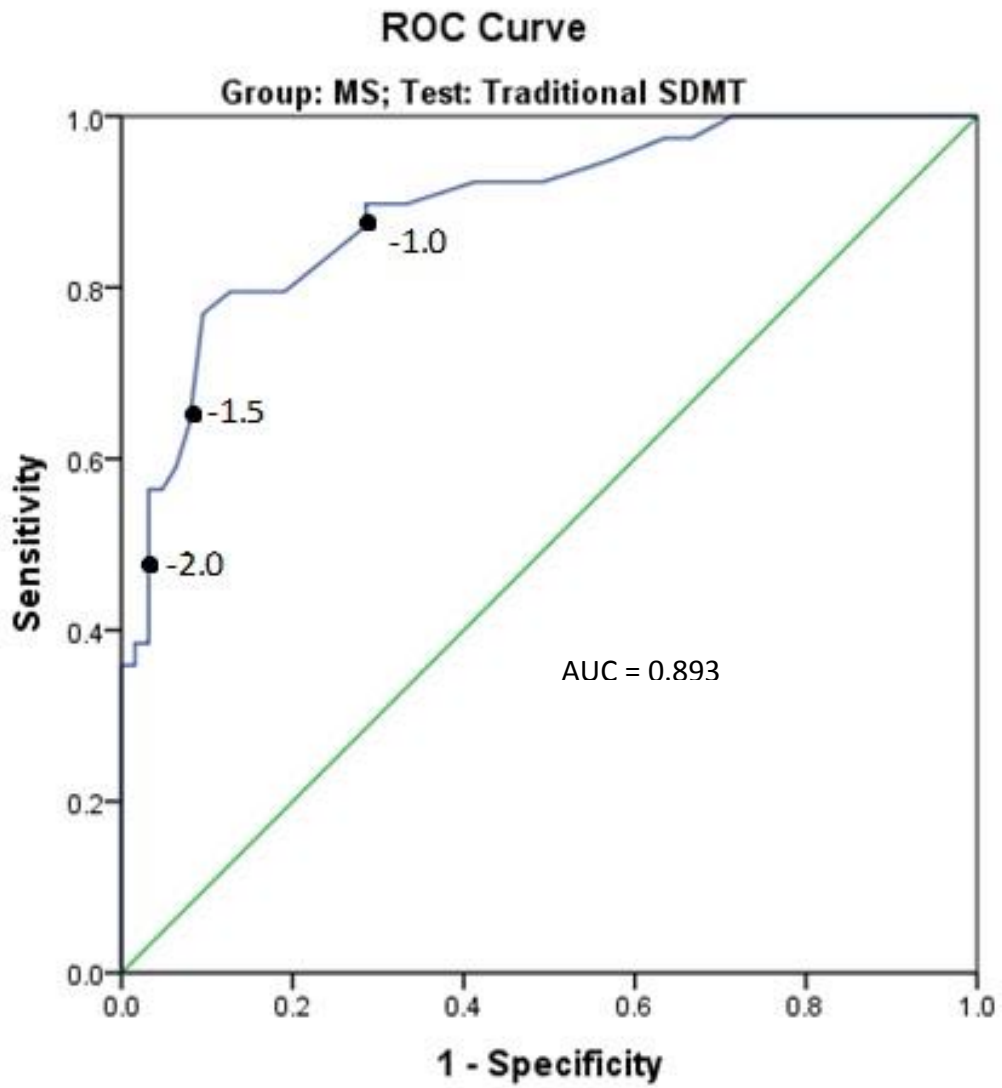
Diagonal segments are produced by ties.

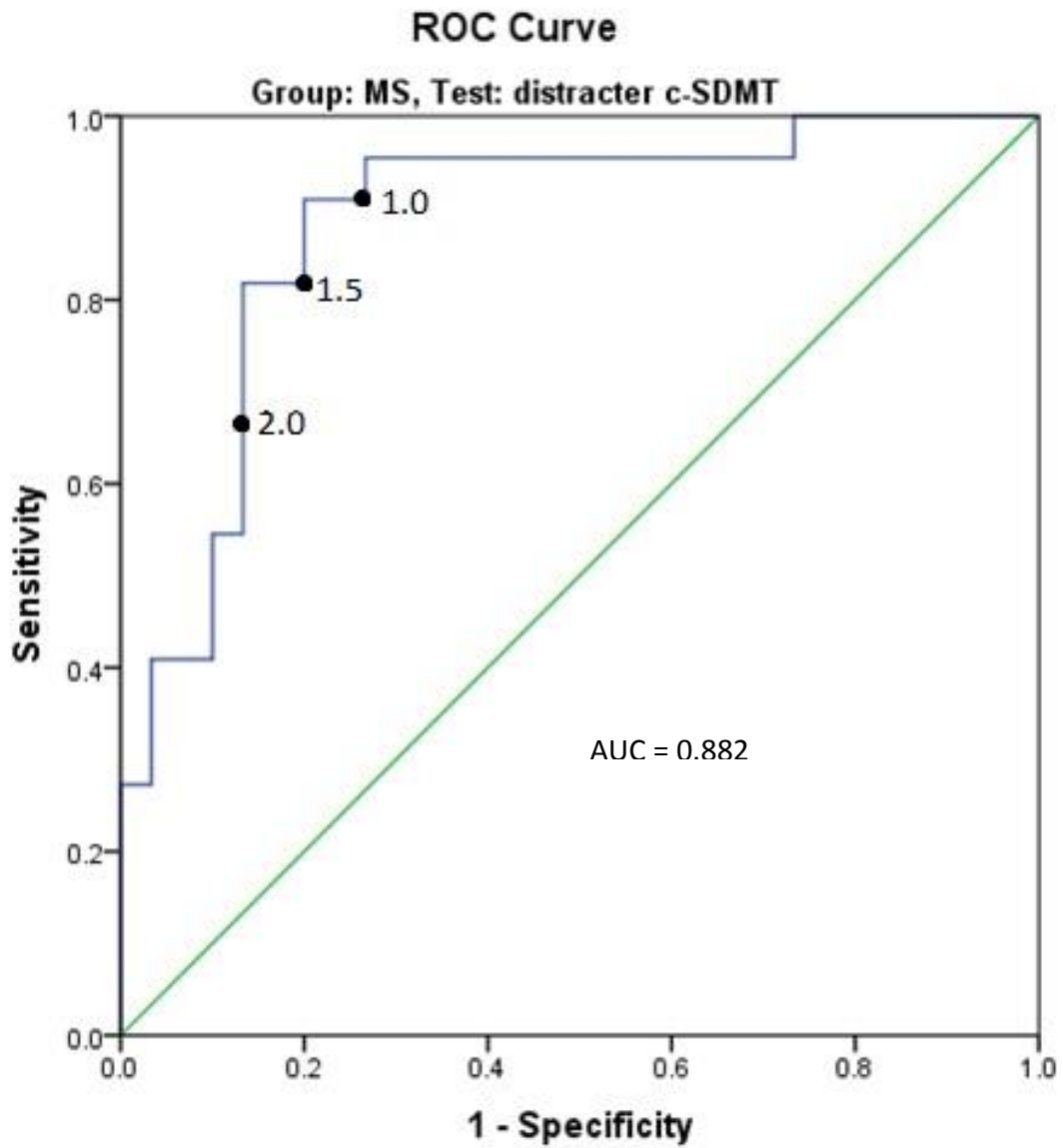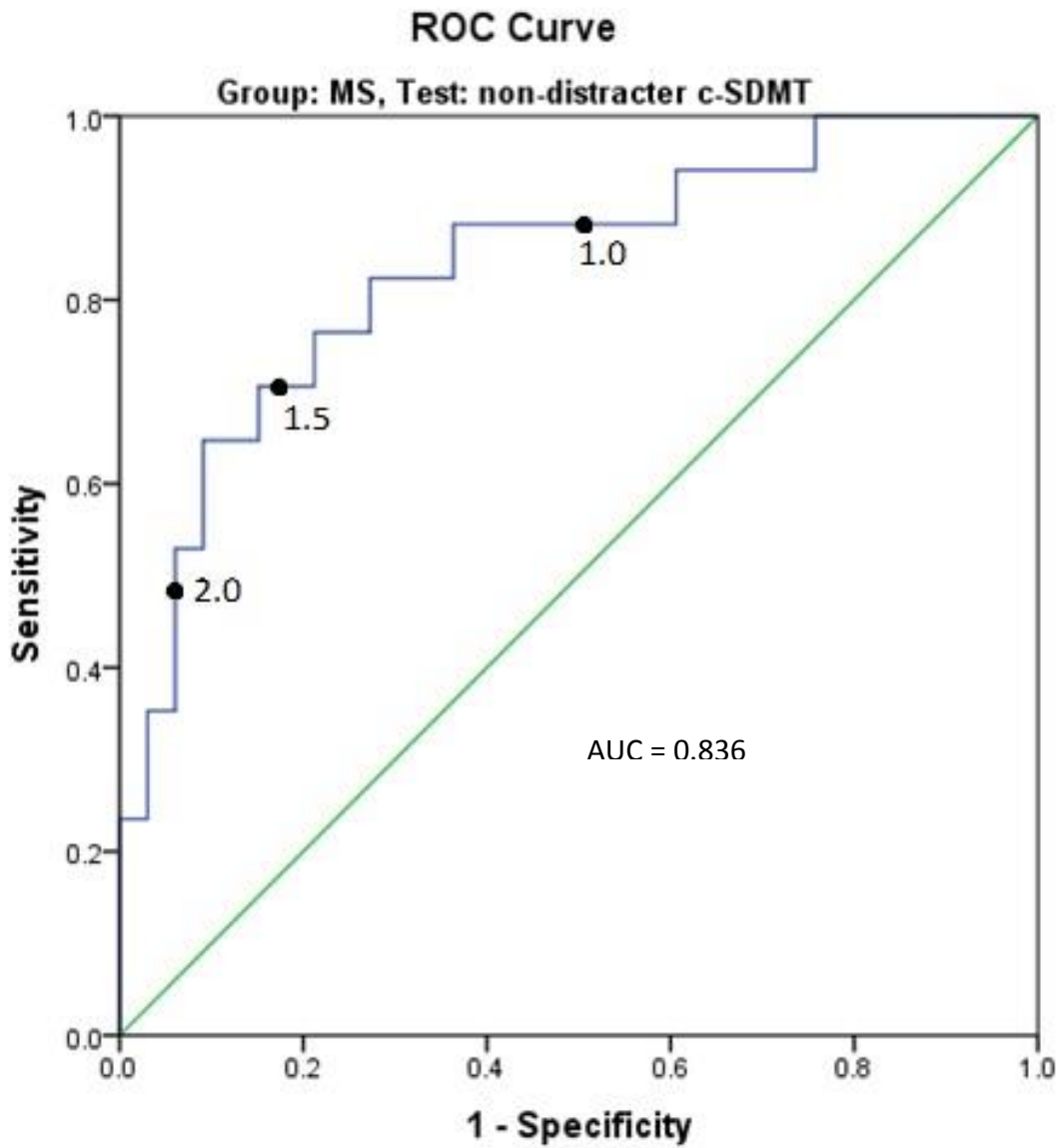**Figure 3: ROC curve for the c-SDMT with distracters in detecting cognitive impairment relative to the MACFIMS**

Figure 4: ROC curve for the c-SDMT without distracters in detecting cognitive impairment relative to the MACFIMS

ROC Curve

Group: MS, Test: non-distracter c-SDMT

AUC = 0.836

3.2.5   Test-retest reliability

Test-retest reliability was ascertained using an intra-class correlation (ICC), two-way fixed model. Twenty-six (25.5%) MS and 17 (24.6%) HC subjects were re-tested after a mean of 100.64 (SD: 10.94) days. Significant ICC coefficients were found for both the distracter (ICC: 0.942, p<0.001) and non-distracter c-SDMT (ICC: 0.918, p<0.001).

3.3   Cognitive reserve and neuropsychological assessment

Based on WAIS-III IQ classifications, 40 (39.2%) MS subjects were classified as having high cognitive reserve and 62 (60.8%) as average/low cognitive reserve. Demographic, neurologic, and psychiatric comparisons between the two groups are shown in Table 5. No significant differences were found, with the exception of the high cognitive reserve group having more years of education and a greater percentage of subjects on disease modifying drugs. Within the high cognitive reserve group, the mean time on the distracter c-SDMT was higher than the non-distracter task, but differences were not significant (15.95 (SD: 5.59) vs. 14.22 (3.03) respectively, z=-0.517, p=0.605). However, the percentage of MS subjects impaired on the c-SDMT with distracters was significantly higher compared to the traditional SDMT (38.9% vs. 15% respectively, x^2=4.074, p=0.044). No significant differences in impairment rates were found between non-distracter c-SDMT and traditional SDMT (22.7% vs. 15% respectively, x^2=0.581, p=0.446) or distracter c-SDMT (22.7% vs. 38.9% respectively, x^2=1.231, p=0.267).

Within the average/low cognitive reserve group, no significant differences in impairment were found between the traditional SDMT and the c-SDMT with distracters (38.7% vs. 50% respectively, x^2=1.144, p=0.285) or without (38.7% vs. 46.4% respectively, x^2=0.475, p=0.491).

As well no differences were present between c-SDMT with and without distracters (50% vs. 46.4% respectively, x^2=0.078, p=0.779).

Level of leisure activity pursuit was also assessed in MS subjects. There were no significant differences in leisure activity pursuit during early 20s or 30s between those cognitively intact and impaired on either the MACFIMS or the distracter c-SDMT (Table 6). Leisure activity pursuit within the most recent year, however, was significantly higher in those cognitively intact than impaired (p<0.001). Cognitive, physical and social leisure differed by cognitive status on the distracter c-SDMT, but on the MACFIMS differences only existed between cognitive and social leisure.

Table 7: Comparison of demographic, neurologic and psychiatric data between MS subjects with high and average/low cognitive reserve

	High reserve – mean (SD) /frequency (%); n = 40	Average/low reserve – mean (SD)/frequency (%); n = 62	t-test/x^2	p-value
Age (years)	45.30 (9.50)	44.16 (10.38)	t=-0.559	p=0.578
Sex (% female)	27 (67.5%)	43 (69.4%)	x^2=0.039	p=0.844
Years of education	15.40 (2.22)	14.44 (2.17)	t=-2.192	p=0.031
Illness duration (years)	11.03 (7.64)	11.03 (8.64)	t=0.005	p=0.996
EDSS	2.81 (2.14)	2.61 (1.97)	t=-0.484	p=0.630
% of disease modifying medication	29 (72.5%)	33 (53.2%)	x^2=3.789	p=0.052
Disease course				
RRMS	29 (72.5%)	42 (67.7%)	x^2=0.260	p=0.610
SPMS	8 (20%)	15 (24.2%)	x^2=0.245	p=0.621
PPMS	3 (7.5%)	5 (8.1%)	x^2=0.011	p=0.918
M-FIS fatigue	39.98 (18.30)	40.23 (17.08)	t=0.071	p=0.943
HADS anxiety	7.23 (3.75)	7.85 (4.29)	t=0.760	p=0.449
HADS depression	5.08 (3.42)	5.76 (3.99)	t=0.892	p=0.375

Abbreviations: EDSS – Expanded Disability Status Scale; RRMS – Relapsing Remitting Multiple Sclerosis; SPMS – Secondary Progressive Multiple Sclerosis; PPMS – Primary Progressive Multiple Sclerosis; M-FIS – Modified Fatigue Impact Scale; HADS – Hospital Anxiety and Depression Scale; PSQI – Pittsburgh Sleep Quality Index

Table 8: Comparison of leisure activity between individuals cognitively impaired versus intact on the MACFIMS and c-SDMT with distracters

	MACFIMS			
	Cognitively intact – mean (SD); n = 63	Cognitively impaired – mean (SD; n = 39	t-test/x^2	p-value
Premorbid IQ (WTAR)	108.13 (6.02)	101.31 (9.78)	t = 3.919	p < 0.001
Leisure Activity Scale				
Early 20s	53.94 (11.23)	51.54 (12.84)	t = 0.992	p = 0.324
Early 30s	45.78 (9.48)	42.43 (11.46)	t = 1.544	p = 0.126
Most recent year	42.56 (8.70)	35.47 (10.15)	t = 3.719	p < 0.001
Cognitive leisure	18.19 (5.38)	14.55 (4.76)	t = 3.437	p = 0.001
Physical leisure	12.75 (4.40)	11.50 (4.60)	t = 1.365	p = 0.178
Social leisure	11.71 (3.29)	9.53 (2.87)	t = 3.392	p = 0.001
	c-SDMT with distracters			
	Cognitively intact – mean (SD); n = 28	Cognitively impaired – mean (SD); n = 24	t-test/x^2	p-value
Premorbid IQ (WTAR)	107.07 (6.07)	102.58 (8.86)	t = 2.096	p = 0.043
Leisure Activity Scale				
Early 20s	55.46 (13.60)	51.46 (11.21)	t = 1.147	p = 0.257
Early 30s	45.08 (10.13)	43.04 (11.24)	t = 0.654	p = 0.516
Most recent year	45.19 (10.07)	34.63 (9.88)	t = 3.770	p < 0.001
Cognitive leisure	19.56 (5.05)	13.75 (4.51)	t = 4.307	p < 0.001
Physical leisure	13.70 (4.48)	11.00 (4.31)	t = 2.189	p = 0.03
Social leisure	11.93 (3.44)	9.88 (3.46)	t = 2.120	p = 0.039

3.4   Influence of anxiety and depression on distracter effects

A cut-off score of 8 or higher on the two subscales of the Hospital Anxiety and Depression Scale (HADS) was used to determine clinically significant depression and anxiety. Based on this cut-off, 29 (28.4%) MS subjects were classified as depressed and 51 (50%) as anxious. There were no differences in demographics or neurological data between MS subjects depressed versus non-depressed and anxious versus non-anxious (Table 7). On both the distracter and non-distracter c-SDMT, depressed MS subjects were significantly slower than non-depressed subjects (Table 8). Significantly more depressed subjects were impaired on the distracter c-SDMT than non-depressed, but this difference was not present for the non-distracter task. There were also no differences in global cognitive impairment based on the MACFIMS by depression. No differences were found on any cognitive tests between MS subjects anxious and non-anxious.

To control for the effects of anxiety symptoms in subjects classified as depressed and depressive symptoms in those classified as anxious, both variables were entered into a linear regression model as putative predictors of performance on the c-SDMT. Depression emerged as a significant predictor, more so on the distracter test (regression coefficient (B): 1.01, p=0.034) than non-distracter (B: 0.475, p=0.053). Anxiety did not predict performance on either distracter (B: -0.525, p=0.264) or non-distracter (B: 0.378, p=0.077) c-SDMT. There was no additive effect of depression and anxiety on distracter (B: 0.244, p=0.236) or non-distracter (B: -0.052, p=0.692) c-SDMT performance.

Table 9: Demographics and neurological data of MS subjects by depression and anxiety

	Depressed – mean (SD) /frequency (%); n=29	Not depressed – mean (SD) /frequency (%); n =73	t-test/x^2	p – value
Age (years)	46.17 (8.46)	43.99 (10.56)	t = -0.994	p = 0.322
Gender (% female)	22 (75.9%)	48 (65.8%)	x^2 = 0.985	p = 0.321
Years of Education	14.34 (1.78)	15.00 (2.35)	t = 1.356	p = 0.178
Premorbid IQ	104.48 (8.73)	105.93 (8.19)	t = 0.791	p = 0.431
EDSS	3.03 (2.13)	2.55 (1.98)	t = -1.709	p = 0.283
Illness Duration (years)	12.69 (9.48)	10.36 (7.63)	t = - 1.292	p = 0.199
Disease Course				
RRMS	18 (62.1%)	53 (72.6%)	x^2 = 1.089	p = 0.297
SPMS	8 (27.6%)	14 (19.2%)	x^2 = 0.589	p = 0.443
PPMS	3 (10.3%)	5 (6.8%)	x^2 = 0.351	p = 0.685
	Anxious – mean (SD)/frequency (%); n=51	Not anxious – mean (SD)/frequency (%); n=51	t-test/x^2	p – value
Age (years)	43.67 (9.91)	45.55 (10.13)	t = 0.949	p = 0.345
Gender (% female)	35 (68.6%)	35 (68.6%)	x^2 = 0.000	p = 0.999
Years of Education	14.94 (2.28)	14.69 (2.16)	t = -0.580	p = 0.563
Premorbid IQ	105.88 (8.04)	105.16 (8.66)	t = -0.438	p = 0.662
EDSS	2.39 (1.99)	2.99 (2.04)	t = 1.499	p = 0.137
Illness Duration (years)	11.53 (7.92)	10.52 (8.57)	t = -0.615	p = 0.540
Disease Course				
RRMS	36 (70.6%)	35 (68.6%)	x^2 = 0.046	p = 0.830
SPMS	10 (19.6%)	13 (25.5%)	x^2 = 0.505	p = 0.477
PPMS	5 (9.8%)	3 (5.9%)	x^2 = 0.543	p = 0.715

Abbreviations: EDSS – Expanded Disability Status Scale; RRMS – Relapsing Remitting Multiple Sclerosis;

SPMS – Secondary Progressive Multiple Sclerosis; PPMS – Primary Progressive Multiple Sclerosis

Table 10: Comparison of cognitive data in MS subjects by depression and anxiety

	Depressed – mean (SD)/frequency (%); n=29	Not depressed – mean (SD)/frequency (%); n=73	Mann-Whitney/ x^2	p – value
% impaired on MACFIMS	15 (51.7%)	24 (32.9%)	x^2 = 3.122	p = 0.077
c-SDMT mean time (seconds)				
Distracters	22.69 (14.04)	16.24 (7.84)	z = -2.676	p = 0.007
Non-distracters	16.91 (4.03)	15.54 (6.15)	z = -2.161	p = 0.031
% impaired on c-SDMT				
Distracters	11/15 (73.3%)	13/37 (35.1%)	x^2 = 6.266	p = 0.012
Non-distracters	7/14 (50%)	11/36 (30.6%)	x^2 = 1.654	p = 0.198
	Anxious – mean (SD)/frequency (%); n=51	Not anxious – mean (SD)/frequency (%); n=51	Mann-Whitney/ x^2	p – value
% impaired on MACFIMS	20 (39.2%)	19 (37.3%)	x^2 = 0.042	p = 0.839
c-SDMT mean time (seconds)				
Distracters	18.20 (10.58)	17.94 (10.12)	z = -0.451	p = 0.652
Non-distracters	15.45 (4.58)	16.21 (6.23)	z = -0.390	p = 0.697
% impaired on c-SDMT				
Distracters	17/32 (53.1%)	7/20 (35%)	x^2 = 1.627	p = 0.202
Non-distracters	5/19 (26.3%)	13/31 (41.9%)	x^2 = 1.247	p = 0.264

Abbreviations: c-SDMT – computerized Symbol Digit Modalities Test; MACFIMS – Minimal Assessment of Cognitive Functioning in Multiple Sclerosis

CHAPTER 4: DISCUSSION

The present study demonstrated that adding distracters to the SDMT increased its sensitivity, in detecting cognitive impairment in people with MS. In comparison to the traditional paper version, the sensitivity of the distracter c-SDMT increased by 18% when using the conventional 1.5SD cut-off. The increase in sensitivity was offset by a lower specificity than the traditional test. Construct validity of the test was evident based on the test's ability to detect higher rates of impairment in people with progressive MS. The test-retest reliability was also robust. Although no statistically significant differences were found between the distracter and non-distracter c-SDMT, MS subjects were on average slower by 2 seconds on the distracter test. This suggests that distracters do interfere with cognitive processing to some extent.

The SDMT was chosen to modify for several reasons. The test is known to be a sensitive marker of cognition in people with MS and results correlate strongly with total lesion volume and brain atrophy. Unlike the PASAT, the other widely used test of information processing speed, the SDMT does not require prior mathematical abilities and people with MS do not find the test stressful to complete. This was confirmed in the present study based on the fact that 15 subjects (15%) were unable to complete the faster 2 second PASAT, whereas all managed the c-SDMT. The SDMT has comparable sensitivity and reliability to the PASAT and serial versions are available to allow repeated testing with minimal practice effects.

The MACFIMS battery served as the 'gold standard' for determining overall cognitive impairment. By convention, global impairment on the battery is defined as a failure on 2 or

more of the 11 cognitive indices. This means that individuals may be labelled as cognitively impaired if they failed a single test in one cognitive domain (e.g. the PASAT 3 and 2 second versions), despite being intact in all other domains. To overcome this limitation impairment thresholds have been varied by researchers. In the present study 15% of MS subjects had missing PASAT data and to avoid defining global cognitive impairment based on failure on one task the criteria was modified to 3 or more cognitive indices.

The computerized version of the SDMT has been validated for use in people with MS (Akbar, Honarmand, Kou, et al., 2011). It was found to have comparable sensitivity and specificity to the traditional test. The present study extends this finding by showing that the sensitivity of the c-SDMT increased by 12% upon adding distracters. The brevity of the c-SDMT makes it highly suitable for use in busy clinic settings compared to other brief assessment tools such as the BRB-N and the BICAMS which take approximately 40 and 15 minutes, respectively. The c-SDMT takes less than 5 minutes to complete and results are provided automatically through the computer, which saves a considerable amount of time scoring. It may also be less influenced by head motion and speed of eye movements than the traditional paper version since the scanning distance between the symbol-digit key and the stimuli is kept fixed for the duration of the task.

The utility of the distracter c-SDMT was further highlighted in the context of high cognitive reserve. Cognitive reserve refers to the individual differences in cognitive processing that allows some people to cope better than others with brain disease and it is associated with a higher premorbid IQ, advanced occupational status and more leisure pursuits. In MS it has been shown to moderate the effects of cerebral atrophy on cognition (Sumowski et al., 2010). Using

premorbid IQ as a proxy for reserve, comparisons between three versions of the SDMT were made within high and average/low cognitive reserve groups. Consistent with the WAIS-III qualitative IQ descriptions high cognitive reserve was defined as a premorbid IQ greater than or equal to 110. The distracter c-SDMT was better able to unmask deficits in the high cognitive reserve group which the other two versions of the SDMT could not. This finding has potential clinical significance since 24% of individuals with high cognitive reserve deemed cognitively intact on the traditional SDMT were found to be impaired on the distracter c-SDMT. The comparable figure for the non-distracter c-SDMT was one third of this. There were no significant differences between the three versions of the SDMT within the average/low cognitive reserve group suggesting that in these individuals cognitive impairment is not as subtle.

Premorbid leisure activity is known to contribute to cognitive status in people with MS independent of premorbid IQ and education (Sumowski et al., 2010). After controlling for brain atrophy, people with MS who participated in more premorbid leisure activities had better current cognitive status. This study limited the assessment of leisure activity to a single premorbid age range, the early 20s, to control for age related differences in lifestyle (e.g. parenting responsibilities in later life). Similar effects of premorbid leisure on cognitive functioning have been reported in the Alzheimer and dementia literature (Sörman, Sundström, Rönnlund, Adolfsson, & Nilsson, 2014; Helzner, Scarmeas, Cosentino, Portet, & Stern, 2007). Leisure activity data in the present study were broken down into different decades (i.e. early 20s, early 30s and the most recent year), which revealed new insights into this aspect of cognitive reserve. In contrast to previous research, no differences in premorbid leisure were

84

found during the early 20s or 30s between cognitively impaired versus intact MS subjects. However, leisure activity pursuit within the most recent year was significantly higher in the latter. This finding suggests that intact cognition is important for maintaining an active lifestyle. Furthermore, cognitively impaired MS subjects were older and had significantly higher EDSS scores than those intact. Therefore, in addition to cognitive status, greater disease burden, older age, and co-morbidities such as depression may also contribute to a decrease in leisure pursuits. Alternatively, these results could also suggest the reverse – that an active lifestyle is needed to keep an intact cognition and that a decrease in leisure pursuits results in depression.

Leisure pursuits are generally classified into cognitive, social and physical activities. While the Sumowski et al. (2010) study limited the analysis to exploring associations with leisure pursuits only in the cognitive domain, the present study extends these findings by reporting on social and physical leisure as well. Differences in the most recent year were present in all three leisure domains between cognitively intact versus impaired individuals. Engagement in cognitively and socially stimulating activities has been consistently associated with a reduced risk of dementia, but recently physical activities have also been shown to have a positive effect (Buchman et al., 2012; Helzner et al., 2007; Williams, 2015). Cognitive benefits from physical activity are thought to arise due to increased cerebral blood flow and nutrient supply.

The present study also revealed that depression adds to the cognitive burden in people with MS, more so than anxiety. Based on a previously established HADS cut-off score, 28% of people with MS were depressed and 50% anxious. In the presence of distracters, the deleterious cognitive effects of depression became more distinct. On the distracter c-SDMT significantly more depressed MS subjects were impaired than non-depressed, but the same was not true for

the non-distracter test. Furthermore, depression emerged as a better predictor of performance on the distracter c-SDMT than the non-distracter. Anxiety, however, did not predict performance on either versions of the c-SDMT

Studies have demonstrated that people with MS are more susceptible to distraction. In the presence of auditory distracters cognitive performance on a working memory task suffers in comparison to the quiet condition (LaPointe et al., 2005). A recent study of inattentional blindness has also demonstrated that MS subjects who failed the Stroop test were not only more likely to be distracted, but also less efficient in tasks involving working memory and executive function (Feinstein et al., 2012). The current study adds to this MS literature by investigating the potential confounding role of depression on cognitive performance amidst distracters.

The relationship between depression and cognition in MS has previously been investigated. Studies have demonstrated that cognitive functioning is further compromised only in the context of severe depression (Demaree et al., 2003). In particular, depression is thought to have an adverse impact on the executive function aspect of working memory. No MS study has investigated the mood-cognition relationship in the presence of distracters, but studies from the general neuropsychological literature have been informative. Greater deficits in selective attention and distracter inhibition have been reported in people who are clinically depressed versus healthy controls (see Epp, Dobson, Dozois, & Frewen (2012) for review). Furthermore, severity of depression has been associated with larger between group effects. Using the emotional Stroop task it has also been shown that depression not only increases susceptibility to distraction, but it also biases attention towards negative stimuli which causes further slowing

of cognition. The emotional Stroop is a modified version of the classic Stroop test in which subjects name the colour of emotionally significant words. For example, words like "death" or "hate" represent emotional stimuli whereas words like "closet" or "wind" are neutral. Unlike the classic Stroop where distraction is due to the incongruence between colour and word, the meaning of the word is not in conflict with the colour. Rather the interference in the emotional Stroop is thought to be due to the emotional salience of the words, which can result in slower response times during colour naming. Studies using auditory distracters have shown similar results. In the presence of sadness induced by a mix of music and autobiographical recall prior to completing an auditory-visual oddball task, distracter effects increased two fold in comparison to the neutral mood condition (Pachecho-Unquetti & Parmentier, 2014). This study adds to these data in the context of a neurological illness. Given that the cognitive effects of distracters are exacerbated in the presence of distracters, current data highlight the importance of diagnosing this co-morbidity. Future studies should investigate whether treating depression brings added cognitive benefits as well.

A limited number of MS studies have investigated the relationship between anxiety and cognition with a recent study showing that state anxiety impacts performance on tasks of executive functioning and processing speed, independently of depression and fatigue (Goretti et al., 2014). However, in this study the PASAT was used as a cognitive measure for processing speed, therefore, it remains unclear to what degree their results were influenced by the anxiety invoking properties of the test itself. General neuropsychological studies have also reported an association between anxiety and memory, attention and executive function, but the literature remains largely inconclusive (Robinson, Vytal, Cornwell, & Grillon, 2013). According to Eysenck's

attentional control theory (2007), anxiety reduces attentional control towards goal-directed tasks and increases attention towards task-irrelevant stimuli. As a consequence of this impaired attentional network, anxious people are easily distracted compared to less anxious people, especially in face of threat-related distracting stimuli (see Eysenck, Derakshan, Santos, & Calvo (2007) for review). No previous study in MS has investigated the cognitive effects of distracters in relation to anxiety. The findings from the present study suggest that there are no differences in distracter effects by anxiety in people with MS.

Limitations

The results of the present study are promising, but should be interpreted with certain limitations in mind. Small sample sizes in subgroup analyses (particularly with cognitive reserve) could have led to type 2 error. Furthermore, the sample of primary and secondary progressive MS subjects was relatively low.

Comparison of same subjects with both the distracter and non-distracter c-SDMT was not possible due to the inclusion of the MACFIMS in the methodology. Although this would have been the optimal approach to ascertain sensitivity of distracters in cognitive testing, the MACFIMS contains the traditional oral SDMT and having subjects complete three versions of the test would have made it difficult to tease apart practice effects on performance. There were no differences in demographics or neurological data between the distracter and non-distracter groups, and while the distracter group was more anxious this did not influence their performance on the distracter c-SDMT.

Practice from the c-SDMT could have influenced performance on the traditional SDMT given the order of testing. In this regard, a counterbalanced methodology was not utilized, where the traditional SDMT was administered first in a subset of individuals. It is important to note, however, that if practice did influence results it would have done so equally for both distracter and non-distracter groups, yet differences only emerged between the distracter test and the traditional SDMT.

The traditional and computerized SDMT measure processing speed with different outcomes, where the former measures the number of correct responses in a given time and the latter measures reaction time. Drawing comparisons between these two tests is important in the context of developing a new and potentially improved version, however, in doing so certain confounding factors may play a role. These may include looking at a computer screen versus a piece of paper, differences in head and eye movements, etc.., but confounders were identical for all subjects and the only methodological difference between groups was the presence of distracters.

Future directions

Future research needs to build on the current study by addressing its weaknesses and incorporating additional facets for enquiry. For the purpose of analysis the current sample was split into distracter and non-distracter groups. Hence, if this methodology is to be replicated, it should be done in a larger sample of MS subjects so that subgroup analyses are not limited by small numbers. Future studies need to be more inclusive of PPMS subjects, as the numbers were relatively low in the current sample. Additionally, a larger sample of healthy controls is

required. If another study replicates the current findings then the c-SDMT with distracters might be the single MS cognitive test of choice and a potentially useful replacement for the PASAT in the MSFC. To ideally assess the sensitivity of distracters in neuropsychological testing, a repeated measures design should be employed where the same subject is tested in distracter and non-distracter condition and order of testing should be counterbalanced.

It also remains unclear whether the c-SDMT with distracters will be good for longitudinal testing since people, having been given the test once, will now anticipate distracters. The test was shown to be reliable after a three month re-test, but future studies need to assess its usefulness over a longer time period. Research has shown that if people are forewarned about potential distracters then cognitive effects are eliminated. For example, there is no impact on memory recall if participants are told before the learning trial that auditory distracters will occur (Hughes et al., 2013). However, in the current study all subjects were told beforehand that they must try and ignore any distracters. Given that cognitive effects on the c-SDMT were still prominent despite the warning, then distracter effects may not be substantially reduced with repeated testing. If distracters are found to be anticipated then parallel versions of the test can be developed that employ different types and frequency of distracters.

The traditional SDMT is shown to be strongly correlated with brain MRI metrics. To further boost the construct validity of the c-SDMT with distracters future studies should investigate imaging correlates of this test and see to what extent it improves the current SDMT brain correlates.

The present study was explorative in nature and therefore distracters were limited to simple environmental sounds presented in 3 out of 8 trials of the c-SDMT. Given that the data show promise, then in theory, introducing stronger distracters, either by increasing the frequency of distracter stimuli or introducing different types of distracters, could elicit greater cognitive effects. Particularly, research in the general population has shown that random, incomprehensible speech is more distracting than environmental sounds, therefore it would be interesting to assess whether the intervention of speech increases the sensitivity of neuropsychological testing even further. It has been theorized that the serial processing of distracter speech significantly interferes with performance on the primary task at hand.

In addition to information processing speed, memory and learning are also frequently impaired in MS and future studies should assess if distracters significantly impact this cognitive domain. Although conventional memory tests, such as the CVLT-II or the BVMT-R, have not been computerized, distracters (either sounds or speech) can be intervened during the learning phase to see if they have an effect on immediate or delayed recall. This has been studied in the general population where the mere presence of sound, either during the learning phase or a short retention interval, significantly impairs serial recall. These effects need to be replicated in the MS population using standard neuropsychological measures.

Another area for future research is in neuropsychological assessment of people with Clinically Isolated Syndrome (CIS) and Radiologically Isolated Syndrome (RIS). Cognitive impairment is frequently reported in CIS and predicts early conversion to full MS. RIS refers to a clinical situation in which lesions suggestive of MS are found by chance on an MRI in individuals who are asymptomatic or 'clinically silent." Although labelled as 'clinically silent' lesions,

neuropsychological studies have shown that individuals with RIS perform significantly more poorly than healthy controls on measures of information processing speed, working memory and verbal fluency (Lebrun et al., 2010). Assessing cognition with distracters in subjects with CIS and RIS could reveal clinically significant deficits not detected with previous methods. This is important because cognitive impairment has been found to predict conversion to full MS in people with CIS (Zipoli et al., 2010).

Information processing efficiency involves both processing speed and working memory, with the former explaining majority of the variance in information processing deficits in MS (DeLuca et al., 2004). The symbol-number pairing key was kept fixed for the duration of the 8 trials in the current study. Therefore, working memory also played a role in task performance. This was evident based on a trend towards a decrease in reaction time across the 8 trails of the c-SDMT (Table 5). Research is currently underway where MS and HC subjects are being tested with a variable c-SDMT, which has the symbol-number key changing for each trial of the test. This methodology removes a working memory component and could be a purer measure of information processing speed.

Conclusions

The present study shows that the incorporation of real-world distracters slows down cognitive processing and increases the sensitivity of a validated computerized version of the SDMT. The traditional psychometric testing environment is far removed from the realities of the working world and the use of distracters can help narrow this ecological divide. Furthermore, as demonstrated, distracters have an additional value in detecting subtle cognitive deficits in

people with high cognitive reserve that are often missed by traditional testing approaches. The cognitive effects of distracters may also be influenced by several factors such as mood and fatigue, which should be taken into consideration when assessing results. Although distracters show promise in neuropsychological assessment of people with MS, future studies need to build on the present findings to further validate this novel approach.

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114

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