THE EFFECT OF AUDITORY DISTRACTION ON INFORMATION PROCESSING SPEED IN RELAPSING REMITTING MULTIPLE SCLEROSIS



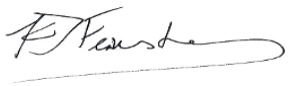
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Declaration

I declare that this dissertation is my own, unaided work. It is being submitted for the degree of Doctor of Philosophy at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other university.



_____

Karen Jennifer Redhill-Feinstein

12th day of June, 2023, Johannesburg, South Africa

This thesis is dedicated to

My family, Ant, Pips, Saulie and Clarrie

my precious life companions.

Having you on this long journey has made it possible.

For your encouragement and patience, deepest gratitude and love

ABSTRACT

Multiple sclerosis (MS) is an autoimmune, neurodegenerative, demyelinating disease, with symptoms ranging from a variety of physical and cognitive impairments to mental health difficulties. It affects younger adults as symptom inception generally occurs in the 20-40 year old range. Cognitive impairment impacts 45% to 60% of the MS population. It can be one of the first symptoms of MS and once diagnosed tends to be linked to more extensive cognitive disability later. Impairment in information processing underlies a number of MS specific cognitive functions and early diagnosis of information processing impairment is essential as it leads to continued monitoring and remediation. Cognition is rarely assessed at neurology appointments, because the neuropsychology test batteries that have been developed specifically to target impairment in the cognitive domains most impacted by MS can be lengthy to administer and require specialist training.

Cognitive assessments when conducted take place in quiet rooms, not reflective of circumstances which confront people with MS in the real-world. People with MS exhibit attentional difficulties and experience problems filtering out distractions. The aim of the present research was to consider ecological validity by embedding auditory distractors, in the form of unintelligible speech, in the two computerized cognitive tests, the SDMT and the Stroop, that have already been validated for people with MS. The hypothesis was that people with relapsing remitting multiple sclerosis (RRMS) who test as cognitively intact on the Minimal Assessment of Cognitive Functioning in Multiple Sclerosis (MACFIMS) still experience cognitive difficulties, which would be unmasked with the distractor SDMT and the distractor Stroop.

Results revealed that the cognitively intact RRMS were significantly slower on the SDMT (with and without) distractors compared to the healthy control group. Within group comparisons showed that the cognitively intact and impaired RRMS were significantly slower on the distractor versions of the two tests. The distractor SDMT and the distractor Stroop are highly sensitive, ecologically valid, brief screening tests that reveal impairment in speed of information processing. The utility and power of these tests is that they can be easily administered at clinic appointments by personnel who require little training.

Key words: Multiple sclerosis, relapsing remitting multiple sclerosis, neuropsychological assessment, information processing speed, attention, distraction, unintelligible speed, SDMT, the Stroop

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ABREVIATIONS

BICAMS – Brief International Cognitive Assessment for Multiple Sclerosis

BRB-N – Brief Repeatable Battery of Neuropsychological Test

BVMT-R – Brief Visual Memory Test – Revised

CNS – Central Nervous System

COWAT – California Oral Word Association Test

CVLT 11 – California Verbal Learning Test 11

D-KEFS – Delis-Kaplan Executive Functions Scale

DTI – Diffuse Tensor Imaging

EDSS – Expanded Disabilities Status Scale

ERP – Evoke-Related Potentials

fMRI – Functional Magnetic Brain Imaging

HADS – Hospital Anxiety and Depression Scale

JLO – Judgment Line of Orientation

MACFIMS – Minimal Assessment of Cognitive Functioning in Multiple Sclerosis

MSFC – Multiple Sclerosis Functional Composite

PASAT – Paced Auditory Serial Assessment Test

PPMS – Primary Progressive Multiple Sclerosis

RRMS – Relapsing Remitting Multiple Sclerosis

SPMS – Secondary Progressive Multiple Sclerosis

STMD – Symbol Digit Modalities Test

Stroop – Stroop Colour-Word Interference Test

WTAR – Weschler Test of Adult Reading

CHAPTER 1

INTRODUCTION

Multiple sclerosis (MS) is an autoimmune, demyelinating disease with neural degeneration that affects individuals differently, with symptoms ranging from a variety of physical and cognitive impairments to mental health difficulties. It is one of the most common neurological diseases of the CNS that is not traumatic in nature. Additionally, it is the most prominent neurological disorder of younger adults as most symptom inception occurs in the 20-40 year old range (Browne et al., 2014; Oset et al., 2020). This is the period in life in which an individual may study, foster and consolidate a career, build financial stability and have a family. Thus, the natural trajectory of life events is often disrupted in people who develop MS. Recent epidemiological numbers from 115 countries including 87% of the people in the world, estimate the number people with MS at 2.8 million, with one person diagnosed every five minutes somewhere in the world (The Multiple Sclerosis International Federation, 2020).

Physical symptoms of MS are commonly expressed as fluctuations in gait and mobility, shakiness, visual difficulties, bladder and bowel problems, numbness and tingling in limbs, spasticity and speech disturbance (Conradsson et al., 2018). However, there are many debilitating symptoms that are additional and/or related to physical symptomology or neuropathology. These are fatigue, which is described as one of the most incapacitating symptoms of the disorder and is observed in 53-90% of individuals with MS; sleep difficulties with prevalence rates of 36%-62%; lifetime prevalence rates in depression of 50%; anxiety rates of 45%; cognitive impairment reported as a prevalence of 45%-60%, with cognitive dysfunction increasing from 30-40% of individuals in the early stages of MS, to 80%-90% in

more advanced and progressive MS and unemployment rates which reach levels of 70%-80% five years after diagnosis (Feinstein, 2007; Strober et al., 2014; Strober, 2018). All of these difficulties are devasting and lead to significant reduction in achieving life goals and in quality of life. The diverse expression of MS in each individual creates an imperative to track the course and expression of the disease, which in turn informs the implementation of suitable medical and remedial interventions. The Expanded Disability Status Scale (EDSS) is used by neurologists in order to quantify and monitor disability progression in MS (Kurtzke, 1983). However, the EDSS has limitations as cognitive impairment is not a feature of this scale, although it can be an early symptom of MS (Amato et al., 2010a, 2010b; Berrigan et al., 2013; Eilam-Stock et al., 2021; Glanz et al., 2012; McNicholas et al., 2018).

Cognitive impairment is not clearly connected to duration nor physical disability, although it is pervasive and potentially a most disabling aspects of MS (Benedict, DeLuca & Enzinger, et al., 2017). Between 45%-60% of those diagnosed with MS struggle with cognitive deficits, which are observed early in the disease process and progress through time (Amato et al., 2008; Amato et al., 2010; Benedict, Cookfair et al., 2006; Berrigan, 2013; Riccitelli et al., 2011; Rinaldi et al., 2010; Summers, Fisniku et al., 2008). In some cases, cognitive impairment may be one of the first symptoms of MS and if present in the early stages it tends to be linked to more extensive cognitive disability later (Deloire et al., 2010).

Cognition deficits in MS cover many domains that are heterogeneous, yet interconnected, and are thus difficult to separate into distinct functions. Common cognitive impairments that occur in MS are in the areas of information processing speed, attention, working memory, executive functioning, visual and verbal learning, and memory (Amato et al., 2010a; Brissart, Morele et al., 2013; Chiaravalloti & DeLuca, 2008; Grzegorski et al., 2017; Meca-Lallana et al., 2021). These deficits have significant ramifications for all aspects of life,

including daily activities of life, interpersonal, social and occupational functioning. Crucially, people with MS who experience cognitive impairments compared to those with only physical symptoms are less likely to be employed (Borghi et al., 2013; Campbell et al., 2017). Working memory and selective attention have been identified as key areas of difficulty in people with MS, however, deficits in processing speed may underlie these difficulties and supersede the efficient functioning of cognitive processes (Anderson, 2012; DeLuca et al., 2004; Kouvatsou et al., 2022). Slowing of information processing is potentially an initial expression of relapsing remitting multiple sclerosis (RRMS). Up to 85% of newly diagnosed people with MS present with RRMS. While physical disability in this group is mild, cognitive disability may be present in up to 35%-40% of cases (De Sonneville et al., 2002). Longitudinal research of people in the initial stages of RRMS revealed that the deterioration observed in information processing speed was a primary intellectual mechanism that reflected a decline in cognitive function, even in simple cognitive tasks, but was not related to physical disability (Berrigan et al., 2013; Glanz et al., 2012; Olivares et al., 2005). Notably, when enough time was allowed in neuropsychological tests of planning, people with MS and healthy controls exhibited similar results. However, when time limits were imposed, the former took much longer to find solutions, signifying difficulties with speed of information processing (Owens et al., 2013). Numerous studies have reported impairment in information processing speed in people with MS (Archibald & Fisk, 2000; 2006; Bergendal et al., 2007; Bodling et al., 2012; Borghi et al. 2013; DeLuca et al., 2004; Denney, et al., 2011; Dobryokova et al., 2016; Genova, Hillary et al., 2009; Grzegorski et al., 2017; Hughes et al., 2011; Johnen et al., 2017; Ruet, Deloire et al., 2013). Early diagnosis of cognition is importance to reveal cognitive impairment in people with RRMS and the present research focused on information processing speed in this population. In real world situations efficient processing speed is necessary for optimal

cognitive functioning, and deficits in processing speed pose significant challenges for people with MS competing in the employment market and completing activities of daily life

Although early cognitive impairment, as evidenced in slowing of processing speed, is in itself not used to diagnose MS, it may be a warning sign and certainly a concern for ongoing cognitive decline. Cognitive impairments may be subtle and difficult to discern unless specific neuropsychological tests are administered (McNicholas et al., 2018; Oreja-Guevara et al., 2019; Schultz et al., 2006). It is now strongly recommended that early and continued cognitive assessments be conducted, so that neuropsychological interventions can be effected (Meca-Lallana et al., 2020; Motyl et al., 2021; Oset et al., 2020). The present research shows that cognitive assessments are certainly possible in a neurologist office using brief tests (Langdon, 2016). Psychometric test results demonstrating cognitive impairment can provide essential evidence to motivate for the implementation of rehabilitation strategies, and adaptive neuroplasticity may follow (Chiaravalloti et al., 2015).

Since the evaluation of cognition is not an aspect of the EDSS nor of initial neurological assessment, many people with MS who have cognitive impairments remain undiagnosed and consequently untreated (Amato, Portaccio et al., 2010; Eilam-Stock et al., 2021; McNicolas et al., 2018). Therefore, it is essential to find efficient assessment tools that are sufficiently sensitive in detecting cognitive deficits early in the disease course. This has led to the development and refinement of neuropsychological assessment batteries specifically aimed at revealing impairment in the cognitive domains most impacted by MS from the initial stages of the disorder. The batteries that are commonly used due to their high validity, which target the cognitive domains most affected in MS, are the Brief Repeatable Battery of Neuropsychological Tests (BRB-N; 30 minutes), the Minimal Assessment of Cognitive Functioning in Multiple Sclerosis (MACFIMS; 90 minutes) and the Brief International

Cognitive Assessment for Multiple Sclerosis (BICAMS; 15 minutes). These tests require trained neuropsychology professionals for administration and to score the batteries. Even the shortest battery, the BICAMS, takes 15 minutes to administer by a trained tester. However, neuropsychology professionals are rarely available in an MS clinic. The present study was aimed at bridging this gap by exploring frequently used assessments of information processing speed that are brief and easy to use.

There are three brief tests of information processing speed that are most utilized in MS research, the Symbol Digit Modalities Test (SDMT), the Stroop Colour-Word Interference Test (Stroop) and the Paced Auditory Serial Assessment Test (PASAT). The PASAT is a cognitively demanding test requiring effort as it not only taps into speed of information processing, but also relies considerably on working memory functions and some mental arithmetic skills. Since information processing speed is only an aspect of the PASAT, the other functions required to compete the test may confound results if the test is used only as an assessment of information processing speed (Lopez-Gongora et al., 2015; Sonder et al., 2013). The Stroop is a supplementary test that is often used in cognitive evaluations in MS. Although it assesses information processing speed it also provides insight into the executive function of the inhibition of distractor information (Denney & Lynch, 2009; Hughes, Denney et al., 2013; Scarpina & Tagini, 2017). Studies over the last two decades have revealed that the SDMT is the most reliable and valid single assessment tool for information processing (Benedict, Smerbeck et al., 2012; Fuchs et al., 2022; Gromisch et al., 2018; Parmenter, Weinstock-Guttman et al., 2007; Sheridan, et al., 2006; Sonder et al., 2013). This extends to MS research, where the SDMT is a particularly sensitive and clean test of information processing speed and is deemed more sensitive than other tests at detecting cognitive impairment in the earliest stages of MS, and at predicting further cognitive deterioration (Brochet et al., 2008; Drake et

al., 2010, Oset et al., 2020). It is the only information processing test that is included in all three neuropsychological batteries for MS mentioned above. Therefore, the SDMT and the Stroop, rather than the PASAT, were the tests that were chosen in the present research to assess information processing speed in people with RRMS. The impetus of this research was to enhance the sensitivity of these two neuropsychological tests that are already used and validated in the MS population. They are easily administered, available in computerized form and require minimal training to administer.

Neuropsychological assessments in MS are typically conducted under 'laboratory-type' conditions, in quiet rooms so that auditory distractions naturally occurring in the environment are excluded (Bendixen et al., 2010). However, in the real-world auditory distractions are ubiquitous as sounds carry and can occur at distance, out of sight and in low light conditions. This is in contrast to visual distractions, which are less intrusive as visual stimuli have to be within the visual field. Also, visual stimulus reaches cognitive processing later than auditory information, which results in visual changes (distraction) that are not relevant to the task at hand being less disruptive than non-relevant auditory stimuli (Bendixen et al., 2010). This is especially important in evaluating the effect of distraction on information processing speed, which is by its nature time sensitive. Research involving cross-modal distraction, revealed that auditory distractors are more potent that visual distractors when visually presented tasks are performed (Leiva et al., 2015). The propensity to auditory distraction might explain why some people with MS, particularly with the relapsing remitting course, who are not cognitively impaired on neuropsychological batteries, exhibit functional difficulties in real world situations; in the workplace and in activities of daily life. An intact attentional system is vital for effective cognitive performance, as part of its function is to filter out distractions, yet up to

40% of people with MS have difficulties in attention (Adler et al., 2015; Clough et al., 2018; De Sonneville et al., 2002).

Few studies in MS have explored the effects of distraction on tests of attention and information processing speed (McCarthy et al., 2005). A study evaluating the consequences of auditory distraction on visual cognitive output in people with RRMS found that subtle cognitive processing deficits may be produced by auditory distraction using four-talker babble, namely, four different speech narratives playing at the same time (LaPointe et al., 2005). In the present research it was proposed that people with RRMS who test as cognitively intact may have impairments in screening out and dealing with auditory distraction. There is no assessment instrument to date that incorporates the effects of auditory distraction on cognition in the MS population. Having identified this gap, the aim of the present research was to embed auditory distractors in the form of unintelligible speech into the two selected computerized psychometric tests, the SDMT and the Stroop, that assess information processing speed and that have already been validated for people with MS. The express purpose was to disrupt sustained and selective attention and to examine the effects on information processing speed. It was hypothesized that by introducing real-world auditory distractors into these tests, the capacity to detect cognitive impairment in the form of slower information processing speed would increase in a cohort of people with RRMS who tested as cognitively intact on the MACFIMS. Thus, the development of greater sensitivity in the measurement of cognitive impairment in people with MS was aimed at elucidating difficulties in cognitive function that would not be detected through existing standard cognitive assessments.

In sum, the theoretical contribution of the current research is that it is an important bridge in connecting current theories of auditory distraction with theories of sustained and selective attentional deficits in MS. The paucity of research in auditory distraction in MS is

enriched by additional research and theoretical links that have been made in this thesis. An alert to cognitive deficits in the form of information processing speed and inhibitions of distractions provided by a brief screening in a clinic, can result in a more complete neuropsychological assessment being undertaken. Practical applications of identification of cognitive impairment can lead to appropriate accommodations made in the workplace and in educational settings, reducing attrition in both. In addition, this can lead to the implementation of targeted cognitive rehabilitation, which could assist people with MS on a long-term basis. Knowledge of such a profile further enables the ongoing monitoring of the disease progression and can support decisions regarding efficacy of medication and rehabilitation treatments.

Chapter Two sets the context for the thesis by discussing the epidemiology, etiology and pathogenesis of MS. MS is the most common neurological disorder in the world that is not traumatic in nature, and has prevalence rates that lie between >2 and < 200/100,00 depending on the country. Canada (the country of origin for the sample in this study) has one of the highest rates in the world at >200/100,000 affecting over 90,000 people. In South Africa the prevalence is far less with up to 5,000 people affected. The worldwide rates of MS are discussed in this chapter. Etiology is influenced by genetic, immunological and environmental differences, and the interaction between them. The pathogenesis of MS is complex, since it is a central nervous system (CNS), inflammatory disorder involving demyelination, brain atrophy of white and grey matter, axonal loss and degeneration. The neuropathology of MS is strongly linked to and correlated with cognitive dysfunction. This chapter also discusses the function of magnetic resonance imaging (MRI), evoked-related potentials, analysis of cerebrospinal fluid, EDSS scores and the use of the McDonald criteria in standardizing MS diagnosis.

Chapter Three explores the cognitive spheres of information processing speed, working memory and attention, and the interface between them in relation to MS. These areas are most often impacted in the initial stages of the disease. Different theoretical models of these cognitive spheres are critically reviewed for their explanatory power. Information processing speed as an underlying cognitive impairment in MS is substantiated by overwhelming research. Information processing difficulties in turn affect attention, working memory, executive functioning, and verbal and visual memory. The impact of auditory distraction on selective attention is discussed together with relevant theoretical constructs. Cognitive load, which impacts information processing is considered, as well as the alerting systems of the brain. The neuropathological origins of these cognitive domains are also discussed.

Chapter Four concentrates on theories conceptualizing selective attention and distraction. The focus of the chapter is on auditory distraction since this is ubiquitous. Sound processing is neurologically obligatory even when attention is directed elsewhere, for example on a target task. People with MS are particularly susceptible to distraction, which can impair performance in both accuracy and speed. Theories of selective attention are examined in terms of early or late selection of perceptual stimuli and their interaction with irrelevant or distraction material. Perceptual load or difficulty encountered in a task is evaluated together with the ability to filter out distractions. Correlates with MS neuropathology are investigated. The potency of the auditory distractor is examined, the most salient being speech, especially irrelevant speech, which necessitates an involuntary bottom-up attentional capture. People with MS have difficulty maintaining focus on a task due to attentional dysfunction. There is a paucity of research on MS and distraction, hence the present study aimed to bridge this gap.

The methodology used in the current study is discussed in Chapter Five. The quantitative research design was quasi-experimental in nature as the RRMS group was divided

into cognitively intact and impaired participants corresponding to their performance on the MACFIMS. The cognitively intact group was then compared to the healthy control group. For within group analyses, a repeated measures design compared each group on the same measures, the Stroop and the SDMT, under two conditions (with and without distractors). Between group analyses evaluated differences on the Stroop and SDMT, with and without distractors between the three groups (cognitively intact RRMS, cognitively impaired RRMS and the healthy controls). The aims and hypotheses are discussed in this chapter, as is the recruitment of the participants and sample design. Assessment instruments are outlined together with the research procedure and ethical considerations. The chapter concludes with a description of the statistical analyses used.

Chapter Six contains a detailed exploration of the results of the statistical analyses. Demographic, multiple sclerosis, mental health and cognitive assessment data (14 subtests) were analyzed for normality of distribution. Bivariate correlations were undertaken to evaluate the relationships between the 14 subtest scores, which confirmed the general structure of the complete assessment battery. The healthy control group was then compared with the total RRMS group. The RRMS was then divided into the cognitively intact and cognitively impaired RRMS groups, based on results of the MACFIMS, in order to test the hypotheses. All cognitive tests were then subject to receiver-operating-characteristic curves (ROC) to establish their sensitivity in separating individuals who were cognitively intact from those who were impaired. Global impairment based on two criteria that were implemented in order to accommodate practice effects is discussed. Results of the groups' performance on the SDMT and the Stroop with and without distractors are outlined.

In Chapter Seven the findings of the current study are integrated with the literature reviewed in the previous chapters, both in terms of comparative research and theoretical

constructs concerning relevant domains of cognition, such as information processing speed, working memory, attention and distraction. These are viewed through the lens of MS, firstly, to critically discuss the present research and secondly, to elaborate on the theoretical debates concerning cognitive impairment in MS. The cross-fertilization of cognitive psychology with the more medically based MS research is able to enhance and broaden the MS cognitive dialectic. The practical implications of the present research are also discussed and strengths and limitations of the study are outlined.

CHAPTER 2

MULTIPLE SCLEROSIS: EPIDEMIOLOGY, ETIOLOGY AND PATHOGENESIS

Introduction

Multiple sclerosis (MS) an autoimmune disease, is one of the most common neurological disorders worldwide and is a significant source of neurological disability that is non-traumatic in etiology. It commonly affects a younger population than other neurogenerative disorders and is typically diagnosed between the ages of 20 to 40, with more progressive courses diagnosed past this period to ages 50 to 60 (Browne et al., 2014; Conraddson et al., 2018). It can develop in the pediatric population as well, which entails a diagnosis before the age of 16. A demyelinating attack before the age of 18 affects about 10% of all diagnosed people with MS (Duignan et al., 2019). MS affects women twice to three times as frequently as men, with the sex difference slowly increasing over the past decades as there is greater diagnostic capability and female longevity (Arnett & Strober, 2011; Jakimovski et al., 2020).

Etiology is influenced by genetic and environmental differences and the interaction between them. The disease is usually diagnosed by clinical presentation and magnetic resonance imaging (MRI). MRI was first used in 1985 as a component of diagnosing MS, and has provided greater reliability in initial diagnosis and subsequent monitoring of progression of the disease process (Kingwell et al., 2013). Although disabling, after 30 years of the disease only one in five in a 26,000 database of people with MS required a wheelchair. However, over 30 years, mobility, hand function, bowel/bladder function, spasticity, cognitive functioning and psychiatric symptoms worsened (Kister et al., 2013). Life expectancy compared to the general population is seven years shorter (Magyar & Sorensen, 2019). Although MS does not

significantly reduce life expectancy, disability, both physically and cognitively, substantially impacts employment, social activities, daily life activities, relationships and general functioning in life (Amato et al., 2008). Many aspects of life are affected by MS and self-esteem tends to be lower in people with MS compared to healthy controls, as are levels of social participation (Mikula et al., 2017). Reduced quality of life is largely due to MS related disability, pain, depression and unemployment (Campbell et al., 2017).

One of the major impacts of MS is on vocation, and unemployment is reported to be in the region of 50% to 80% within 10 years of initial diagnosis, which results in lower levels of economic status, poorer self-esteem and reduced cognitive and social stimulation (Morse et al., 2013; Strober, 2020). Cognitive impairment in MS contributes to more withdrawal from work than physical impairment (Campbell et al., 2017; McNicholas et al., 2018). Not only do those affected with MS experience difficulty finding employment, but also in sustaining work (Calabrese, 2006). Since cognitive functioning is related to the ability to retain employment, cognitive impairment in MS is a predictor of deteriorating vocational ability (Macaron et al., 2020). The onset of MS symptoms usually occurs between ages 20-40 when a career is starting and developing, thus clinically definite MS results in a loss of career identity, work productivity, career satisfaction and financial security to the majority of individuals. Employment status is related to test scores that assess information processing speed (such as the SDMT) and overall cognitive impairment is related to unemployment (Macaron et al., 2020; Morse et al., 2013). In addition, a decrease in multitasking ability was related to worse occupational outcomes and vocational status seven years after being diagnosed with MS, and was predicted by cognitive deterioration during this time and by slower information processing speed (Morse et al., 2013; Ruet, Deloire, Hamel et al., 2013). A systematic review was conducted in order to investigate the link between high rates of reduced work hours or

unemployment in people with MS and cognitive impairment (Clemens & Langdon, 2018). Thirteen studies met the inclusion and exclusion criteria. The most frequently researched cognitive area was information processing speed followed by immediate recall. Twelve of the studies reported a relationship between unemployment and cognition. Numerous studies revealed that information processing speed was linked to employment status, and the SDMT was the test most frequently used to identify slower processing and to assess work trends, such as early retirement and reduced hours. The SDMT seems to be the most effective test at linking cognitive ability to employment status, thus poorer performance on this test is a predictor of unemployment (Campbell et al., 2017; Macaron et al., 2020). The Paced Auditory Serial Assessment Tests (PASAT 3 and 2)[1] were able to discriminate unemployed and employed people with MS, however were not as sensitive at distinguishing work trends. Impaired performance on the Brief Visual Memory Test – Revised (BVMT-R) reflecting poor visual memory recall was associated with unemployment with similar results on the California Verbal Learning Test – 11 (CVLT-11) reflected significantly poorer verbal memory. Different tests of executive function revealed few differences in performance as a whole between the employed and unemployed (Clemens & Langdon, 2018). The SDMT is a sensitive measure in detecting cognitive dysfunction, which is frequently reiterated in the literature. It is predictive not only of employment status, but of the status of general cognitive competence, which is the reason for its inclusion in the present research.

The number of people diagnosed with MS differs significantly across populations and approximately 2.8 million people are affected in the world (The Multiple Sclerosis International Federation, 2020). Incidences of the disease are highest in Caucasians of Nordic

[1] The PASAT, BVMT-R and CVLT-11 are part of the MACFIMS the neuropsychological battery used in the present researh

origins and are not as common in other racial groups. The highest incidences are noted in Western Europe, the British Isles, Scandinavia, the Italian peninsula, Central and Eastern Europe, and people of European descent in North America (Howard et al., 2016; Koch-Henriksen & Sorensen, 2010). In terms of concentration and landmass many of those in the world affected by MS live in Europe.

This chapter first explores the epidemiology and etiology of MS, which is followed by the pathogenesis of the disorder and means of diagnosis. It is important to understand the manner in which damage to the brain caused by the disease process impacts cognition, therefore, the connection between brain pathology and subsequent cognitive dysfunction is considered. Cognitive impairment may be mitigated by cognitive reserve and this process is also investigated. Cognitive impairment and cognitive functions most affected in MS will be examined in Chapter 3.

Epidemiology

Epidemiology research provides the information necessary to understand the presence and distribution of MS in the world and to track changes over time. This research has become additionally refined as more sophisticated diagnostic measures are developed and further treatment options become available. Globally, numerous epidemiology studies of populations affected by MS have been undertaken, however, many of these studies have not been methodologically rigorous as different diagnostic measures have been used. MRIs were first introduced in 1985 to enhance accuracy in the diagnosis of MS and this was the starting point for reliable epidemiology statistics. The metanalytic study detailed below stipulated as an inclusion criterion that only studies post-1985, with MRI results, be reviewed. Meta-analytic research has been carried out in order to evaluate the most useful, sound studies so that a more accurate estimation of the status of MS epidemiology worldwide may be gained. A major meta-

analytic research project was initiated in 2012 to understand the global distribution of MS (Kingwell et al., 2013). The research protocol was developed by an international research community. It evaluated a particular chosen diagnostic system, the McDonald Criteria (which will be detailed later), the representation of the researched population and how well it was defined, as well as the reliability and completeness of the data. Of the 3,256 international studies found online, only 183 met the inclusion criteria, indicating that only about six percent of the papers were sufficiently academically rigorous. The research papers were then divided into three zones, Europe, the Americas, and a third mixed zone, Africa, Asia, Australia and New Zealand (Kingwell et al., 2013; Mahkani et al., 2014). In the following meta-analytic study, the standard of the quality of the research was evaluated separately by two trained reviewers utilizing an extensive scoring rubric. This review is important in that it specifies the magnitude and distribution of MS worldwide and further provides contextual information about the extent of MS in Canada, which is one of the highest in the world.

The proportion of people affected by MS in a particular region may either be referred to as incidence rate or prevalence rate. The prevalence rate refers to the number of people diagnosed with MS, within a region at the time of the study. Incidence rate refers to new clinically definite diagnoses of MS in a single year and provides a narrower scope of understanding the number of people with MS at a specific time (Koutsouraki et al., 2010). Prevalence and incidence rates are expressed per unit of population, typically per 100,000 people. The World health Organization (WHO) has provided a prevalence rate of 35 per 100,000 and an incidence rate of 4 per 100,000 worldwide for MS (Bezzini & Battaglia, 2017). The range of the prevalence rates lie between > 2 and < 200/100,00 depending on the country, although there are some outlying prevalence ratios of < 2 in China and >200 in Canada, Scotland Ireland, Finland and Sweden. Most studies that were part of the meta-analysis of the

three regions of the world included prevalence rather than incidence rate (Kingwell et al., 2013; Makhani et al., 2014). Thus, in the present research the prevalence rates of MS will be discussed. It is important to consider that most prevalence rates do not include an entire country and so in many instances regional numbers rather than entire countries are reported (Magyari & Soelberg, 2019). This creates some difficulty examining population-based estimates and may underestimate MS numbers as there is a dearth of research in particular regions, such as Africa, Australasia and South America.

It is interesting to note that migration in early life skewed the individual towards the risk of acquiring MS, mirroring the adopted country, whereas in migration after age 15 the individual retained the risk characteristic of their country of origin (Pugliatti & Ferri, 2020). This is in contrast to a Canadian study which found that the greatest risk to increased development of MS occurred in those from the Middle East with longer habitation in Canada and was linked to increased risk even in adulthood (Rotstein et al., 2019). So environmental exposure even in adulthood may contribute to higher risks of MS development.

In the following section an overview of prevalence rates will be explored in the three geographical zones in the metanalytic research, namely, Europe, the Americas, and a third mixed zone, Africa, Asia, Australia and New Zealand

Europe

There are more than 600,000 people with MS in Europe (Bezzini & Battaglia, 2017). A meta-analytic study by Kingwell and colleagues (2013) reviewed research into the epidemiology of MS in Europe. They found 123 studies fitting the inclusion criteria, using the criteria elucidated previously. Eight regions were included, namely, the Italian Peninsula and Malta; the British Isles; the Nordic region; the Iberian Peninsula; Belgium, France and Netherlands; the Central European countries; South East Europe; and the Baltic States,

including Russia (Kingwell et al., 2013). Prevalence in women was noted to be 1.8 – 2.4 percent higher than in men. The most studied regions were the Italian Peninsula and British Isles. One of the highest incidences of MS globally is in Scotland and Northern Ireland with a prevalence of more than 200 per 100,000 (10^5) in the population, followed by southern Finland and Northern Sweden. The Iberian Peninsula contained the greatest incidence in the Valencia region in Spain, namely 70 per 10^5 people and in Italy the rate was averaged at 176 per 10^5 (Battaglia et al., 2017; Kingwell et al., 2013). The highest prevalence in France ranged from 95 to 150 per 10^5 of the population and in Belgium 80 to 90 per 10^5. In South-East Europe incidences of MS all fall lower than the rates mentioned previously, ranging from 50 per 10^5 in Bulgaria, to 150 per 10^5 in Northern Bulgaria and 120 per 10^5 in Western Greece. These prevalence rates underscore the variability of MS populations in Europe, but are none-the-less high compared to other regions of the world (Kingwell et al., 2013). There were few studies of ethnic differences in prevalence of MS, however, research in Norway conducted on 786 people with a definite diagnosis of MS revealed only 27 MS participants (10%) from the Middle East, Asia and Africa. Prevalence of MS was high in the Norwegian/Western Group ($170/10^5$) and lower in the Asian ($21/10^5$) and African ($20/10^5$) cohorts (Smestad et al., 2008).

Africa, Asia, Australia and New Zealand

Studies of MS incidence and prevalence in Africa, Asia, Australia and New Zealand are relatively uncommon and 28 studies found were included according to the criteria. There were 21 from Asia, two from Africa and five from Australia and New Zealand (Makhani et al., 2014). Half of the studies evaluated were mediocre, probably related to difficulty in obtaining MRIs and the low number of neurologists per capita in the poorer nations. The observed prevalence of MS in Australia was $50\text{-}57/10^5$. In Tasmania a prevalence of $100/10^5$ was determined and in New Zealand the prevalence rate was $102/10^5$ in those of European descent

and $24/10^5$ in the Maori population. Prevalence in Asia was particularly divergent and was lowest in Hong Kong at $0.77/10^5$ and highest in Turkey at $101/10^5$. Studies in Iran were variable depending on region from 4 - $60/10^5$. In India prevalence was $15/10^5$, in Japan 9 – $10/10^5$ and in Korea $4/10^5$. In Israel a study found that the prevalence of immigrant European or American Jewish people was $64/10^5$ compared to African or Asian Jewish people which was $22/10^5$. The prevalence was least in Israeli-born Arab people, $19/10^5$. Meta-analytic research undertaken in the last decade in Pan-Asian countries found that MS prevalence per 100,000 population compared to the study by Makhani et al. (2014) had increased in Japan from 13 to $16/10^5$, in China from below 1.0 to $1.39/10^5$, in Hong Kong to $14.8/10^5$ (Eskandariah et al., 2016). There appears to be only one published epidemiological study of MS numbers in South Africa. This covered one area in South Africa, KwaZulu Natal, home to 9.9 million people. Different race groups were studied and results based per 100,000 population were white South Africans, $26/10^5$ (more prominent among English speakers compared to Afrikaans speakers); Indian South Africans, $8/10^5$; mixed ancestry South Africans, $1.94/10^5$; black South Africans, $0.22/10^5$ (Bhigjee et al., 2007). Modi et al. (2008) extrapolated numbers with the help of the MS Society of South Africa (MSSA) for the entire country and reached a number of 5,000, of whom just less than 90% were white South Africans similar to the numbers described by Bhigjee et al. (2007). This number reflects the population distributions described by Koch-Henriksen and Sorensen (2010).

The Americas

A meta-analytic study of the prevalence of MS in the Americas reviewed research in North, Central and South American regions (Evans et al., 2013). Inclusion criteria were met by 31 studies, 25 of which were from the North American regions. Only nine studies were located in the USA mostly reporting prevalence for the eastern regions and ranged from $40/10^5$

in Texas to $191/10^5$ in Minnesota. Six studies in Central and South America revealed that the lowest prevalence was reported in Panama, $5/10^5$ and the highest in the Argentine Patagonia area at $17/10^5$. The number of people with MS in Canada is approximately 90,000, in a population of 38 million. Prevalence of MS in Canada ranged from $56/10^5$ in the east of the country (Newfoundland) to $298/10^5$ in Saskatchewan. A nationwide study found a prevalence of $240/10^5$. These numbers reveal that the highest incidence of MS worldwide is found in Canada, well surpassing the elevated numbers in Scotland, Northern Ireland and Scandinavia. The sample of people with RRMS for the current study was drawn from the Canadian population.

The specific cause of MS is unknown, but is alleged to be a mix of genetic, environmental, and immunological influences. The next section discusses what is established about the etiology of MS.

Etiology of Multiple Sclerosis

Etiology refers to causes or origins of a disorder and there are no known exposures, neither genetic nor environmental that provide indisputable evidence for MS causality. However, genetic factors are easier to research than environmental exposure, the latter of which varies greatly over time and between individuals (Goodwin, 2014; Sawcer, 2011).

In terms of the environment, latitude has historically been identified as causing a variation in MS with higher prevalence (as noted in the previous section) in Europe, North America, Australia and New Zealand. Part of this latitude gradient may be related to lower exposure to UV radiation in the winter months and therefore, reduced absorption of vitamin D. Low vitamin D intake is thought to be related to a greater risk of MS relapses when MS has already been diagnosed and perhaps even influences the development of an immune reaction *in vitro* (O'Gorman, Lucas et al., 2012).

Infections have been investigated as another source of pathogenesis (O'Gorman, Lucas et al., 2012). The most consistent finding in relation to the increased risk of the occurrence of MS is the Epstein-Barr virus, also known as infectious mononucleosis (Hedstrom et al., 2020). Higher rates of antibodies against this virus were found in people who had MS in comparison with a matched healthy control group (Woulk et al., 2021). Individuals who contracted mononucleosis prior 18 years old had an eight times risk of MS diagnosis (Compston, 1999). Smoking also increases the risk of autoimmune diseases, an example being MS, as neurotoxic components of cigarette smoke cause tissue damage. Diet, obesity and intestinal microbiota are additionally positively connected with an increased risk of developing MS. Excessive dietary salt is known to affect systemic anti-inflammatory responses. Changes in sleep pattern from shift work and general disruption in circadian rhythm may be supplementary causative factors in the genesis of MS (Matveeva et al., 2018).

Strong evidence implies that genetic features predominate over environmental influences in earlier onset of the disease (O'Gorman, Lin et al., 2012). To date the genomes of 47,351 people with MS have been compared to 68,284 controls and 233 variants have been found, attesting to the complexity of the genetic etiology of MS (Compston, 2020). Incidence and prevalence rates are higher in family members of those with MS (Patsopoulous, 2018). Genetic data revealed that there was a recurrence rate of approximately 15% in families for developing MS (Compston, 1999). The rate is greatest for siblings (3%), followed by parents and children (2% each). A study was conducted in Canada with 370 twin individuals with MS, comprised of 120 males and 250 females. Concordance rates were investigated between monozygotic and dizygotic twin sets and their non-twin siblings. Blood samples were taking from each twin to determine whether they were monozygotic or dizygotic. The concordance rate for monozygotic twins was 25.4% (22 out of 24 pairs were female) and for dizygotic twins

5.4%, with the rate for non-twin siblings at 2.8% (Willer et al., 2003). The result implies that the closer the genetic associations are, such as in monozygotic twins, the greater the likelihood of developing MS.

The pathogenesis and neuropathology of MS will be discussed in the following section, from the earliest stage of MS which is identified by myelin inflammation and breakdown. This complex process leads to lesions, which over time become chronic and eventually result in atrophy in different regions of the brain. Although physical disability is typically a hallmark of MS, the focus of this research is on cognitive impairment and the discussion on neuropathology will be associated with known impacts on cognition.

Pathogenesis of Multiple Sclerosis

Multiple sclerosis is a chronic, autoimmune, disorder of the CNS causing inflammation, affecting the brain and spinal cord, involving both demyelination and degeneration. The pathophysiology of MS is distinguished by chronic inflammation, blood-brain barrier breakdown, immune cell attack and damage to the myelin sheath of axons, resulting in axonal loss (Matveeva et al., 2018; Ron, 2018). It is distinguished by lesions or area of neuronal damage, also known as plaques. Since damage may occur in different areas of the brain and spinal cord, the presentation is highly varied. Post-mortem results have provided a sequential chronicle of MS, beginning as a focal inflammatory disease with plaques or lesions, which over time changes to diffuse inflammation and greater, progressive demyelination, axonal damage and areas of brain atrophy (Feinstein, 2007). After the acute inflammatory stage, the MS lesions may go into a chronic phase that can include remyelination, inflammation that may resolve, but also a state in which myelin degeneration, repair and inflammation co-occur (McGinley et al., 2021). People with MS show increased bilateral brain activation compared to controls in the frontal cortex, parietal and temporal lobes and right cerebellum, in tasks

related to working memory, attention and executive functions such as planning and problem solving (Chiarovalloti & DeLuca, 2008). To effectively maintain performance, this new or increased activation may include neuronal reorganization and recruitment of other regions of the brain to sustain cognitive and physical functioning (Julian, 2011). However, even if compensatory recruitment occurs the system may be less energy efficient (Coggan et al., 2015). None-the-less in the earlier stages of MS before the disease burden is too great, there is a complex balance of neuronal damage, repair and cortical reorganization (Rocca et al., 2016).

Historically MS was deemed to be a white matter disease, however, it is now well accepted that there is significant involvement of cortical, grey matter damage, constituting cortical atrophy and lesions, which are strongly linked with cognitive impairment (Macaron et al., 2020; Papathanasious et al., 2013; Rossi et al., 2012). Calabrese et al. (2015) argued that the origins of grey matter injury and its connection to white matter damage in MS remains uncertain and the question often raised is; does cortical atrophy occur as a consequence of white matter lesions or does it occur simultaneously? It appears that grey and white matter demyelination may coexist separately, however, there is some association between white and grey matter damage, since neuronal degeneration inevitably results from axonal lesions. In some cases of MS there is predominantly grey matter pathology and in others the opposite is found. There is also evidence that there is a primary grey matter degenerative process independent of inflammation and white matter damage. However, further research in that area is ongoing (Calabrese et al., 2015). Both grey and white matter lesions are found early in the disease process in RRMS. A group of people with early RRMS were studied over a two-year period to investigate cortical and white matter lesion. Both types of lesions co-occurred and in this time there were considerably more white matter lesions than cortical lesions, with some new lesions, others resolving, shrinking, stabilizing or those with chronic activity. It was

observed that when lesions repair there was a correlation with positive cognitive changes in sustained attention, processing speed and cognitive flexibility (Todea et al., 2020). This indicates that in the initial phases of RRMS when brain injury is resolved, functioning both cognitive and physical can return to previous levels.

The following sections will investigate neuroanatomy, exploring nerve cell structure, the MS disease process in white matter, white fibre tracts, grey matter and deep brain structures. All of these brain components are implicated in cognition and when damaged result in impaired cognition. Figure 2.1 is a diagram of the various structures of the brain that exhibit MS disease injury and that play a part in cognitive impairment.

White Matter and the Process of Inflammation

Axons or nerve fibres are covered by a white, fatty myelin sheath that gives rise to the component of the brain called white matter. The myelin sheath insulates and separates each fibre allowing for speed of signalling and prevents intersection of neuronal firing. Neuronal cell bodies are largely devoid of myelin and are grey in colour with an overlay of capillaries, hence named grey matter. Grey matter does none-the-less still contain myelin, connecting cells to one another to maintain signal conduction.

The defining feature of the process of MS is an inflammation of the myelin sheaths of the axons, which results in demyelination, causing a reduction in neurological function and slowed or interrupted relay of information between parts of the brain (Kutzelnigg et al., 2005; Simons & Nave, 2016). The interruption of neurological signals in white matter results in reduced speed of information processing. Speed of information processing is a significant underlying aspect to which other cognitive spheres such as working memory, attention and various diverse modalities of memory depend.

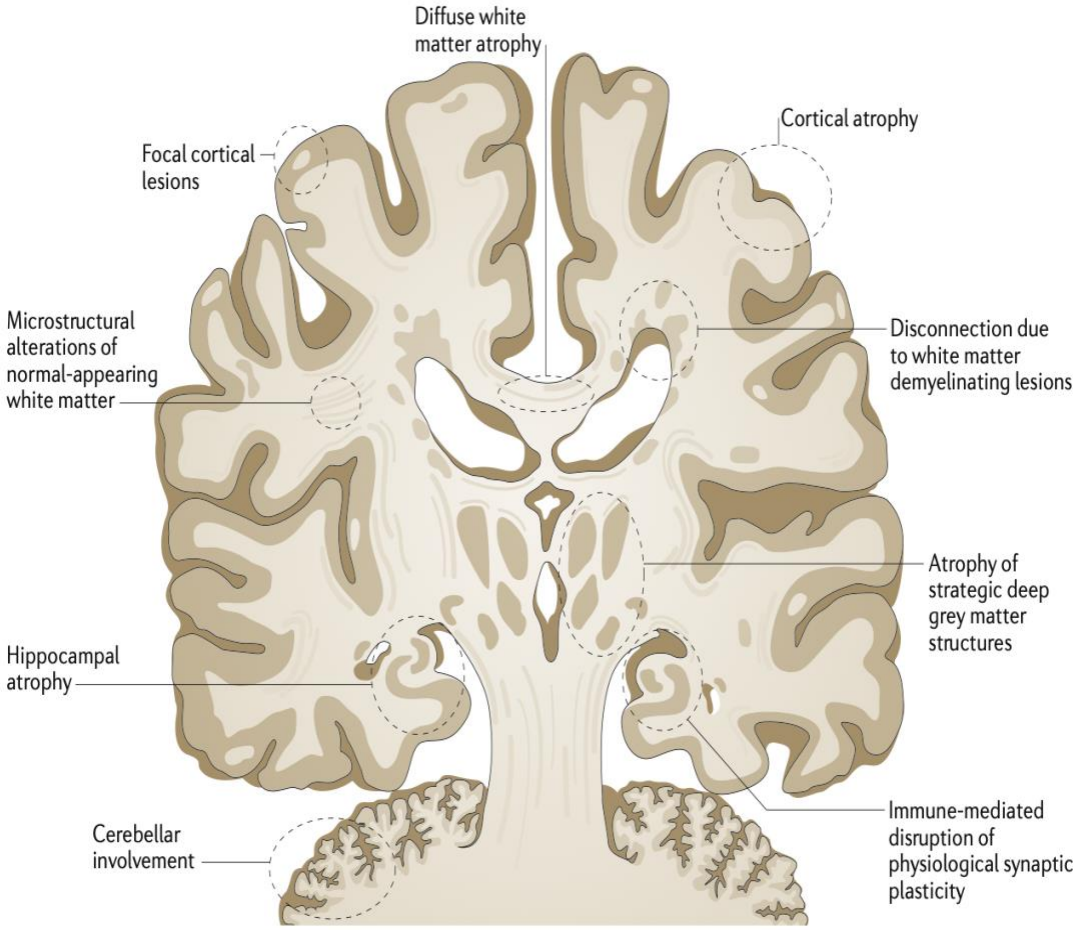


Fig. 1 | **Putative mechanisms underlying cognitive impairment in multiple sclerosis.** Various factors may contribute to cognitive impairment in multiple sclerosis. In white matter, focal demyelinating lesions, microstructural alterations in normal-appearing white matter and diffuse atrophy may interrupt neuronal pathways between brain areas strategic for physiological cognitive functioning, leading to a 'disconnection syndrome'. At the same time, a role is played by diffuse and focal cortical pathological changes and dysfunction in specific structures, such as deep grey matter nuclei (including the thalamus), the hippocampus and the cerebellum. A pathogenic role may also be played by immune-related disruption of long-term forms of synaptic plasticity, such as long-term potentiation. Background image inspired by Figure 13.17A in REF.[149].

Figure 2.1

Mechanisms Underlying Cognitive Impairment in Multiple Sclerosis. (Di Filippo et al., 2018). Multiple sclerosis and cognition: Synaptic failure and network dysfunction. *p. 602, copyright Nature Reviews. Neuroscience, 2018).*

The SDMT is acknowledged as especially sensitive to decreased information processing speed in MS and is a key aspect of the present research. Over the past few years the SDMT is regularly utilized as a choice neuropsychological assessment of information processing speed in MS. There is compelling data associating changes in SDMT scores to cognitive functional decline during acute disease relapse and to changes in neuropathology (Benedict, DeLuca, Phillips, et al. 2017; Riccitelli et al., 2019). Since MS is a demyelinating disorder it is important to provide details about the anatomy of myelin and the process by which myelin becomes damaged due to failure of the immune system.

Myelin and MS Pathogenesis

Myelin is a lipoprotein made up of oligodendrocytes which wrap in a spiral formation around the axons of cells in the CNS forming a plasma membrane, which acts as an electric insulator (Simons & Nave, 2016). Oligodendrocytes are not only myelin producing cells, but additionally supply trophic support which helps to develop and maintain neural connection between nerve cells (Dulamea, 2017). Myelin oligodendrocyte glycoprotein also ensures the structural integrity of the myelin sheath. The process of myelin inflammation and demyelination occurs when the immune system malfunctions and the oligodendrocytes are targeted by this system. T cells and B cells are white blood cells of the immune system (lymphocytes) and perform a vital function in the adaptive immune response. They manufacture antibodies that fight invading pathogens such as viruses and bacteria. The prevailing theory for the pathogenesis of MS is that T and B cells form and react as an immune response against myelin antigens. Antigens in this case are toxic or foreign substances (such as viruses or bacteria) which cause immune responses in the CNS (Kipp et al., 2015; van Langelaars et al., 2020). B cells recognize antigens and secrete antibodies in an endeavour to neutralize the pathogen. T cells become activated by this process and react directly against the

antigen in the lymphatic system. They cross the blood-brain barrier, which is a membranous barrier that separates brain tissue from circulating blood and is formed by endothelial cells of the capillary wall. In the CNS blood capillaries are covered by endothelial cells that are sealed without pores and are structurally different from other tissue capillaries. The blood brain barrier only becomes permeable during inflammation. Activated T cells are particularly potent and able to break though the endothelial cells into CNS tissue, by releasing chemicals that cause inflammation. This then triggers a more protracted autoimmune response. (McGinley et al., 2021; Ortiz et al., 2014). When active white matter lesions are examined both B and T cells exhibit significant proliferation and are densely massed. An example of an invading antigen is the Epstein-Barr virus. Changes in oligodendrocyte glycoprotein are associated with B cells infected with Epstein-Barr virus, which increases blood brain barrier breakdown and allows through highly activated B and T cells resulting in an inflammatory response (Woulk et al., 2021).

Usual inhibitory mechanisms which regulate adaptation and equilibrium in the immune response are impaired in people with MS. T cells are present in most people, but their presence in people who are at risk for developing MS results in a hyperproliferation of these cells and uncontrolled immune responses that cannot be suppressed (Woulk et al., 2021). Relapses and remissions have been correlated with decrease and increase in the frequency of T cells (Fletcher et al., 2010). When the autoimmune reaction is initiated it leads to myelin production impairment and damage to the myelin sheaths and neurons. It exposes the underlying axons to the inflammatory process resulting over time in axonal and neuronal loss (Demetriou, 2005). This process leads to compromised nerve conduction and the intersecting of neuronal signals, ensuing in delayed or completely impeded nerve impulses. The white matter (axonal) damage consequently changes the neural structure of the brain. The areas of demyelination are typically

multifocal and can involve the brain, spinal cord and optic nerves. (Lazeron et al., 2006). Acute inflammatory demyelinating attacks cause clinical relapses and result in chronic cognitive and motor dysfunction and in increasing neurodegeneration (Moccia et a., 2016). Once the inflammatory response resolves, either spontaneously or with the aid of medication, some myelin regeneration may occur especially in the relapsing remitting disease course (Kutzelnigg et al., 2005). The biochemical and pathobiological process is extremely complex and the full explanation of pathology is beyond the scope of this research. For further details please see Coggan et al. (2015), Fletcher et al. (2010), Ortiz et al. (2014) and Van Langelaars et al. (2020).

Neurological damage due to MS that results in cognitive impairment is due to white matter lesions, demyelination and degeneration in nerve fibres, grey matter degeneration and atrophy in the cortex and deep brain structures. The following section will explore the paths of brain tissue injury and associated impact on cognition.

White Matter Pathology and Link to Cognitive Impairment

White Matter Fibre Tracts

All parts of the brain are linked by white matter fibre tracts and their integrity is vital for normal brain interconnectivity and functioning. When fibre tracts are damaged nerve conduction is impeded, the significance of which depends on the degree of damage. White matter tracts are classified into three groups. Projection fibres which connect cortical regions with deep grey matter, the brain stem, cerebellum and spinal cord. Association fibres that connect different cortical areas in the same hemisphere and support many brain functions and neural pathways. Lastly commissural fibres which connect similar cortical areas and brain structures between the two hemispheres. The largest commissural fibre is the corpus collosum and it connects the entire left and right hemispheres (Wycoco et al., 2013). The corpus collosum has high myelin content and is especially sensitive to demyelination and axonal loss.

It is frequently impacted in MS and focused demyelinating lesions and degeneration are commonly observed from the initial phases of the disease. Additionally, when lesions and degeneration are observed in areas of high axonal matter the course of MS is more aggressive earlier in the process (Granberg et al., 2015). Neuroaxonal loss occurring in the early phases of the MS disease process and the rate of progression of brain injury in corpus callosum lesions and degeneration are associated with consequent brain atrophy. The extent of damage is then predictive of future progression of the disease and cognitive deficits later in the disease course (Papadopoulou et al. 2013). Additionally, neuronal loss affects a number of commissural fibres that are used in attention and information processing speed and correlate with cognitive decline in MS (Summer & Fisniku et al. 2008).

Cognitive impairment associated with white matter fibre tract damage cannot be adequately explained by pathology revealed in conventional MRIs, which feature macroscopic brain damage, but can be further elucidated by microstructural damage. This microstructural injury is revealed in Diffusion Tensor Imaging (DTI) which will be described later in the chapter and is connected to cognitive dysfunction, particularly in information processing speed, executive tasks, verbal and visual memory (Genova et al., 2013; Hoogs et al., 2010; Llufriu et al., 2012; Santiago et al., 2007). Abnormalities in the microstructural integrity of the corpus collosum result in disconnection in conductivity between the hemispheres. It is the disconnection between brain areas, that arises in specific focal areas in white matter regions in the commissural fibre tracts and long projection fibres, that is implicated in cognitive impairment. Cognitively impaired individuals with MS had twice the number of lesions than those who were cognitively intact with the most important lesions for impairment located in the commissural fibres (Altermatt et al., 2018; Rossi et al., 2012). Measurements based on differences in microstructural white matter integrity determined by DTI could distinguish

people with MS who were cognitively intact and impaired (Benedict et al., 2013). From the opposite perspective, research reveals the that preservation of normal functioning connectivity is important for the maintenance of intact cognition despite structural brain damage (Fuchs et al., 2019).

Additionally, information processing speed is related to decreased neuronal conduction speed secondary to demyelination (Guimaraes & Sa, 2012). Significant neurophysiological differences were revealed on fMRI, between controls and MS participants, when they completed information processing tasks. People with MS had slower results as cognitive load increased and used different circuitry compared to healthy controls (Smith et al., 2012). Over a 17-year follow-up study most participants originally recruited were people with RRMS with two-thirds converting to secondary progressive MS (SPMS) over this period. Corpus callosum atrophy was robustly related to decreased speed in challenging information processing tasks such as observed on SDMT scores. Therefore, the strong association of scores on the SDMT and corpus callosum injury and degeneration is a strong endorsement of the use of the SDMT, as it is such a sensitive tool for revealing and monitoring cognitive impairment in the form of reduced speed of information processing.

The SDMT, the Stoop Test and White Matter.

Pertinent to the present research, Yu et al. (2012) found that the SDMT was more sensitive to white matter tract damage that other studies have validated other neuropsychological tests and this finding. Poor performance on the SDMT is also significantly correlated with brain atrophy and lesion load (Glanz et al. 2012). White matter lesion volume in RRMS was a significant predictor of poor SDMT performance, compared to cortical lesions, indicating a stronger association of white matter structural damage with slow information processing speed and working memory. Poor SDMT scores were linked to high lesion

frequency in white matter (Rossi et al., 2012). Studies have also utilized the Stroop test to assess cognition in relation to nerve fibre functioning. When assessing slower processing speed on the Stroop it was found that white matter tracts were vital for connecting brain regions involved in executive function, especially inhibition which was highlighted in the Stroop test (Santiago et al., 2007). Slow information processing speed on the Stroop was found as a cause of lower scores rather than impairment in executive functioning, which is required for response inhibition (MacNiven et al., 2008).

Grey Matter and Deep Brain Structures and Link to Cognitive Impairment

Grey matter is different from white matter as it is predominantly composed of cell bodies with relatively few myelinated axons and is present in the brain, the brainstem, the cerebellum and the spinal cord. However, demyelination can still occur as there are connecting white matter fibres between brain structures and each neuron has an axon. The surface of the cerebral hemispheres, the cerebellum, and deep grey matter structures for example, the thalamus, hypothalamus, basal ganglia, putamen, globus pallidus and septal nuclei, contain a concentration of grey matter. As well as white matter inflammation and damage, brain atrophy is observed in the initial stages of the disease affecting subcortical and cortical grey matter (Sbardella, Petsas et al., 2013; Todea et al., 2020). As previously discussed, although MS is largely characterized by lesions in the white matter of the brain and spinal cord, MRI and neuropathology studies show that a high percentage of inflammatory lesions are also found in the grey matter, especially the cerebral cortex (Rinaldi et al., 2010). It appears that white matter lesions or subtle damage leads to local grey matter damage and in RRMS particular areas of grey matter atrophy are connected to lesion pathology in neighbouring white matter. The cortical damage, both focal and diffuse, progresses over time and is only partly related to white matter injury. Cortical thinning of approximately 10% is found in people with MS compared

with controls (Filippi, Rocca, Horsfield et al., 2013). Cortical demyelination is also common in the initial phases of MS and is inflammatory in nature rather than neurodegenerative. It negatively impacts cognition and has been linked to impairment in memory, attention and information processing speed (Curti et al., 2018; Lucchinetti et al., 2011). Later grey matter damage is also affected by connected, damaged cortical or deep grey matter, resulting in increased atrophy over time and this becomes an independent pathological process (Benedict, DeLuca & Enzinger, 2017). As the disease progresses, grey matter atrophy development increases and may be greater than white matter damage (Sbardella, Petsas et al., 2013). Post-mortem studies have augmented understanding of disease progress; as white matter abnormalities change from being mostly focal and periventricular to being more diffuse, they are associated with a large increase in the degree of demyelination in grey matter (Filippi et al., 2010).

Lesions and Atrophy

Lesion mapping is a critical tool for the evaluation of disease distribution load and size of brain lesions. This allows for domain specific information regarding lesion load to be correlated with specific cognitive deficits. Magnetic resonance imaging studies indicate a substantial number of inflammatory lesions are located in the cerebral cortex of people with MS. It is notable that cortical lesion in the initial phases of MS are inflammatory and not primarily neurodegenerative in cortical grey matter (Lucchinetti et al. 2011) However, these cortical lesions are associated with neuropsychological deficits and the greater the lesion load the more significant the cognitive impairment (Rinaldi et al., 2010).

Although damage to white matter tracts reduces information processing speed it appears that cognitive impairment in RRMS patients with mild disease progression is best explained by atrophic changes rather than lesion load. Brain atrophy may occur in all stages of

MS as a result of inflammatory demyelination and irreversible damage to neurons (Amato, Zipoli et al., 2006; Beck & Reich, 2018). Atrophy is able to be identified early in RRMS and the extent of atrophy soon after diagnosis in RRMS in cortical and deep brain structure is a measure of disease burden. Therefore, the monitoring of atrophy can have a predictive outcome with regard to progressive disability. The capacity of the CNS to compensate and accommodate to the loss of axons and neurons depends on the location of the atrophy and if there is available brain reserve capacity (Zivadinov & Bakshi, 2005), which will be discussed later in the chapter. Once atrophy has occurred it is irreversible and is illustrative of the most damaging neuropathology in MS (Filippi et al., 2010). It is a good prognostic indicator of subsequent long-term neurological impairment and associated cognitive impairment. Even abnormalities in brain matter that appear normal, may contain subtle atrophy as revealed on DTI, and result in cognitive impairment (Sanchez et al., 2008). As grey matter atrophy increases in the course of the disease, cognitive performance decreases and this atrophy is more prominent in people with MS who have cognitive deficits than those who are not impaired (Amato, Zipoli et al. 2006; Lanz et al., 2007).

Cognitive slowing is particularly observable in tasks that demand greater cognitive functioning as revealed by information processing tests, which include the SDMT and the Stroop, rather than simple reaction time, and this is significantly correlated with brain volume reduction (Lazeron et al., 2006). As the brain atrophies and shrinks, volume is lost. Morgen et al. (2007) found that in comparison to healthy controls, people with RRMS showed volume reduction in areas of the left temporal and frontal cortex, which have been determined as regions principally impacted by diffuse neural atrophy in MS (Morgen et al., 2007). The findings revealed that cognitive impairment in working memory, attention and speed of information processing, was closely associated with grey matter cortical atrophy. In a study

aimed at predicting cognitive changes over seven years, diffuse brain damage and central brain atrophy were found on MRI analysis only two years after diagnosis (Deloire et al., 2011). Cognitive domains such as, memory and speed of information processing in MS were positively correlated with grey matter atrophy, cortical-lesion burden and decreased cortical depth. Abnormalities in grey matter tissue microstructure were directly related to deficits in decision-making (Mulhert et al., 2014).

Grey matter atrophy is significantly involved in impairment in the regions of the thalami, insula and temporo-occipital lobes. This is especially implicated in information processing speed, psychomotor speed, visuospatial memory, learning, mood, and motivation amongst others (Deppe et al., 2016). The following section explores the impact of MS on deep brain structures and the effect on cognition.

Deep Brain Structures Affected by Multiple Sclerosis.

People with RRMS have most damaged brain tissue involvement and early volume loss in deep grey matter structures, including the thalamus, hypothalamus, hippocampus and basal ganglia, rather than the widespread and diffuse cortical gray matter damage found in later stages of MS when the disease burden is greater. The basal ganglia and thalamus have a crucial function in effective information processing, and even in the early stages of MS they exhibit a reduction in volume (Batista et al., 2012; Deppe et al., 2016). Batista et al. (2012) have concluded that atrophy of these deep grey matter structures significantly contributes towards slower and less efficient visual and auditory information processing speed in MS. In addition to atrophy, decreased volume in deep grey structures was associated with some reduction in information processing speed, which was consistent with modest disruption of distributing networks involved in cognitive performance (Debernard et al. 2015). These authors also found that white matter lesions contributed to deep grey matter abnormalities.

The thalamus transmits sensory and motor signals, influences consciousness and vigilance, and also integrates functions from a number of brain structures; the midbrain, diencephalon, hippocampus, cortical and subcortical regions (Wolff & Vann, 2019). Thus, as a nerve relay hub it has many reciprocal connections to the cortex and subcortical regions. The thalamus also integrates higher cortical and executive functions and has more recently been described as contributing to cortical functioning and higher-order cognition extending to learning, memory and flexible adaptation (Rojas et al., 2018). It also has a function in selective attention and thus, the capacity to filter out distractions (Fama & Sullivan, 2015). As MRI techniques become more sophisticated, there is the development of greater understanding of the thalamus. Thalamic lesions are more visible on MRI than cortical lesion as they contain a higher density of myelin (Amin & Ontaneda, 2021). Connections can therefore, be made between areas of damage and associated dysfunction. Damage to the thalamus and its varied connections impairs a multitude of neurological functions with wide ranging effects, and is significantly related to declining cognition (Kipp et al., 2015). Deppe and colleagues (2016) determined that very early in the MS disease process there were microstructural areas of damage in the thalamus. Although no actual lesions were present, the volume of the thalamus was reduced by up to 10%, therefore, decreasing thalamic connectivity. Thalamic atrophy, which resulted in reduced grey matter volume was responsible for most variation in cognitive decline in MS as measured on the MACFIMS and was also a strong predictor of cognitive decline in MS (Benedict et al., 2013; Kipp et al. 2015). Functional MRI is able to measure changes in blood oxygenation over time and in this way can show an unusual increase in thalamic activation. Thalamic activation together with thalamic atrophy are the best indicators of decreased information processing speed, memory and executive function in MS (Koini et al., 2016). Benedict et al. (2013), gathered DTI data measuring the integrity of myelin and

axions within the thalamus, as well as thalamic volume measures to assess thalamic atrophy. They found that both grey matter atrophy and white matter damage independently impacted neuropsychological results. There was significantly less volume of the thalamus in MS participants who developed impaired cognition after being followed up for two years. Specifically, attentional deficits correlated with volume loss and there was a strong association between impairments in attention and speed of information processing and T2 lesions metrics and loss of grey matter volume (Rojas et al., 2018).

In addition to the thalamus, atrophy has also been found in the deep grey matter structures of the hippocampus and putamen in RRMS participants and is related to poorer cognitive functioning (Debernard et al. 2015). Hippocampal initial microstructural changes and then atrophy are also involved in learning and memory impairment. Of all the structures, the hippocampus was especially impacted by the consequences of inflammation on synaptic performance and cognitive processes (Di Filippo et al., 2018).

There is also an association between neocortical volume and multiple cognitive domains (Benedict, Bruce, et al., 2006). Specifically, the reduction of grey matter volume bilaterally in the prefrontal cortex is associated with cognitive dysfunction, in information processing speed, attention, working memory and long-term verbal memory (Nocentini et al., 2014). Neocortical volume loss has been more closely associated with cognitive impairment than whole brain atrophy, and cognitively impaired people with RRMS have a higher cortical lesion load and cortical atrophy than those without impairment (Rinaldi et al., 2010). The extent of cortical inflammatory lesion load and neocortical volume loss in people with RRMS was significantly correlated with cognitive deficits, compared to cognitively intact people with RRMS, and these markers were predicative of cognitive decline (Benedict, Bruce et al., 2006; Sinnecker et al., 2020). Riccitelli et al. (2011) found definite patterns of damage in deep grey

matter structures and T2-visible lesions in cognitive deficits in people with RRMS, which were association with deficits in planning, attention, information processing speed, and verbal and spatial memory.

Ventricular enlargement is commonly linked to neurodegeneration and brain atrophy (Millward et al., 2020). As the brain atrophies ventricles become enlarged, which is especially pronounced in the lateral ventricle proximal to the thalamus (Sinnecker et at., 2020). Consequently, an enlarged third ventricle, can be substantially attributed to atrophy of the thalamus (Kipp et al., 2015). The ventricular system as a whole is comprised of a set of four interconnected, communicating cavities within the brain, which are responsible for the production, transportation and removal of cerebrospinal fluid, which bathes and cushions the central nervous system. Ventricular volume is found to fluctuate intermittently in RRMS patients leading to blood brain barrier disruption and inflammation. When this barrier breaks down it allows immune cells to enter into the CNS and this leads to inflammation triggering demyelination and neurodegeneration, which has been discussed previously (Millward et al., 2020). It appears that impaired memory performance is observable early in the RRMS disease course and is associated with alteration in ventricular size (Hildebrandt et al., 2006). Sanchez and colleagues (2008) found that the measurement of third ventricle width was the most substantial indication of general deficits and specific cognitive dysfunction in attention and processing speed, and is a marker of cognitive decline.

With the increased sophistication of MRI techniques diverse brain pathology underlying cognitive impairment is revealed. The next section examines the use of MRI which is used in the diagnosis and ongoing evaluation of stability or progression of the disease. The use of functional MRI (fMRI) has also been extensively used to understand different regions of the brain that are associated with cognitive tasks.

Magnetic Resonance Imaging and Multiple Sclerosis

Magnetic resonance imaging is the technique used in MS for identifying demyelinating lesions. MRI does not utilize radiation, and is more sensitive and non-invasive than CT or conventional X-ray. In terms of diagnosis, it is able to detecting MS pathology and related abnormalities in the brain and is five to ten times more sensitive than clinical data in assessing the activity of the disease (Filippi et al., 2010). Consensus guidelines have recently been developed to promote the widespread use of a standardized MS MRI protocol, which allows for more accurate follow up of disease monitoring, and also for internationally standardized research (Saslow et al., 2020). Magnetic resonance imaging has capability to reveal MS lesions including edema, inflammation, demyelination and axonal loss (Zivadinov & Bakchi, 2005).

MRI sequences use different radio frequencies and timing for the two classes of images used, T1 and T2 weighted images. T1 weighted scans show tissue with high fat content such as myelin that appear vivid, and compartments with cerebrospinal fluid that appear darker. On a T2 scan the opposite occurs when cerebrospinal fluid compartments appear bright and tissue with high fat content (white matter) appears dark. Areas of inflammation which are the first signs of MS pathology typically show up as hyperintense (increased brightness) in a T1 weighted image in a periventricular (area located deeply within the brain) distribution. Generally, a T1 weighted image shows cerebral anatomy distinctly, whereas a T2 weighted image is more suitable in detecting pathology such as MS plaques, overall disease burden or lesion load, both old and new. Hyperintense lesions on T2-weighted images show up due to increased water content and can also detect inflammation, edema, demyelination, remyelination and axonal loss. T2 hyperintensities often occur in cerebral white matter (McGinley et al., 2021). They are likely to result in wide-spread or global neuro-behavioural deficits (Benedict, Bakshi et al., 2002). A contrast medium, Gadolinium-DTPA, is frequently

used to detect disease activity as it enhances images, revealing acute, active inflammation indicative of breakdown in the blood-brain barrier. Gadolinium is a large molecule that usually does not pass the blood-brain barrier. In circumstances where inflammation exists and the barrier is compromised the Gadolinium can pass in and reveal the inflamed area. Gadolinium increases the sensitivity in detecting new T2 lesions and is thus able to mark disease activity even if the T2 lesion load is high (Haider et al., 2019). If Gadolinium is not used then dark areas (hypointensity) indicate areas of permanent damage.

FLAIR (fluid attenuated inversions recovery) derived images are also used to further understand individual disease status and progression, detecting flow of cerebrospinal fluids or lack thereof, and can bring out hyperintense periventricular lesions that are characteristic in MS (Feinstein, 2007). Additionally, the end products of inflammation, namely, degenerative lesions also known as 'black holes', can be revealed. These lesions are hypointense (darker than surrounding tissue) and are detected by T1-weighted scanning parameters. They also indicate severe tissue disorganization, with irreversible brain damage and are synonymous with axonal destruction (the extent of demyelination and changes in axonal density) and degeneration (Filippi et al., 2010).

Although conventional, structural MRI is well utilized and accepted in diagnosing and monitoring the progression of MS, it is not particularly refined in delineating specific brain pathology. Rather, conventional MRI is most often used to examine areas of atrophy and general volume loss (Penner et al., 2007**).** Regions in the brain may appear normal (normal appearing matter) on T2-weighted images, but are damaged and not visible using this type of imaging (Roca et al., 2008). Specialized MRI is able to reveal pathological changes that are not discernable with regular MRIs, such as, neurodegeneration in normal appearing white matter and grey matter. For this purpose, diffuse tensor imaging (DTI) is utilized to determine

whether myelin cells are damaged at a microstructural level. DTI computes the restricted dispersal of water in tissue to produce neural tract or white matter images. Results are calculated measuring the of movement of water molecules in neuronal tissue. In healthy tissue water is free moving, however, pathology that alters normal brain structure affects and restricts water motion and diffusion indexes can be calculated with DTI data (Sbardella, Tona et al., 2013). The resulting consequence is the identification of disrupted white matter tract structural integrity and provides related quantitative metrics. DTIs are also capable of differentiating tissue damage in grey matter that appears as normal (non-lesional tissue) if viewed on conventional MRI (Maranzano, et al., 2020). Using DTI, results revealed that damage to myelin, occurred across cognitively vital white matter tracts and led to decreased neuronal interaction in particular areas that supported cognitive operations, such as processing speed, visual memory and working memory (Yu, et al., 2012). Results from conventional MRI and addition information provided by DTI are complementary and augment information concerning different types of brain damage caused by the disease process (Sbardella et al., 2013; Rossi et al., 2012). In comparisons of cognitively impaired and intact participants with MS, white matter changes were detected using DTI. Damage was identified in areas particularly relevant to cognitive processes, such as the corpus collosum, anterior thalamic radiation, and forceps minor, which constitutes a white matter fibre bundle which attaches the surface of the frontal lobe across the midline of the corpus callosum. The impaired MS participants exhibited decreased functioning on information processing speed and executive functioning compared to the intact participants (Genova et al., 2013). DTI has therefore been promoted as a powerful tool in detecting and monitoring cognitive impairment in MS.

Magnetization transfer imaging (MTR) is another method of examining pathology in white matter, normal appearing white matter and grey matter (Maranzano et al., 2020). MTR

is able to index the capacity of macromolecules to exchange magnetization with the surrounding water, allowing for an estimation of tissue damage. It is a method of looking at the integrity of myelin within white and grey matter lesions as myelin is composed of 40% water (Moccia et al., 2020; Simons & Nave, 2016). The MTR values are reduced in individuals with MS compared to healthy controls.

Positron emission tomography (PET) is also a prominent imaging technique used, that is able to identify ongoing disease pathology by capturing cell body and synaptic alterations. It is a specialized technique requiring specific expertise, but is costly and relies on radiation (Bagnato et al, 2020). Therefore, information obtained by conventional and specialized MRI is easier to access and can be compared over time to follow the trajectory of lesion activity and measurements.

All the MRI measures described above, enable greater understanding of disease pathology and implications for cognitive impairment, however, it is functional magnetic resonance imaging (fMRI) that permits observation of changes in neural organization which develop early on in the disease course. It additionally provides information about the neuroplasticity of the brain and certain changes that reflect cortical reorganization (Amato et al., 2008). fMRI calculates the blood-oxygen level and blood flow associated with neuronal activity in the brain that is activated by motor, sensory or cognitive tasks. It is also able to follow patterns of brain recruitment (Filippi & Rocca, 2013). fMRI changes correlate with the extent of damage to normal appearing white and grey matter in the brain. Data from fMRI studies imply that cognitive dysfunction is the result of neural damage and also, a progressive inability of the capacity of the brain to adapt to increasing damage (Rocca et al., 2015; Rocca et al., 2016). In order to determine cognitive functioning and which areas of the brain are recruited in cognitive tests, such as the PASAT, SDMT, the Stroop test and tests of executive

function, fMRIs are routinely used. Early in the disease course, during cognitive tasks observed during the fMRI process, people with RRMS employ additional brain regions or show greater activation within the same regions compared to healthy controls, which signifies adaptive cerebral reorganization to compensate for disease associated damage (Ghaffar & Feinstein, 2007; Rocca et al., 2014).

The brain is an adaptive organ and repairs and reorganizes neural activity to function as optimally as possible. There is individual variation in brain reorganization and the following section explores the concept of cognitive reserve and the conditions that create the most advantageous conditions for neurological adaptation.

Cognitive reserve

Cognitive reserve can be defined as additional cognitive capacity developed as a consequence of higher educational attainment, enriched vocabulary, which is tapped in tests of premorbid IQ, occupational achievement and engagement in stimulating leisure activities that contain an intellectual component. These have been found to be cognitively protective, cushioning the effects of brain degeneration (Ruet & Brochet, 2013). A definition of cognitive reserve is that it is the mental resilience or resistance to the effects of structural brain damage (Fuchs et al., 2019). It is based on the concept that the brain can compensate for damage by transferring cognitive functions from areas of injury through neural networks to more intact areas (Schwartz et al., 2013). Some people are able to tolerate significant disease load and neuropathology experiencing little cognitive dysfunction, and it is the concept of cognitive reserve that can explain the incomplete association of structural brain injury and MS cognitive functions (Fenu et al., 2018).

Approximately a third of people with MS (including all disease courses)[2] do not experience cognitive impairment. A meta-analytic study based on rigorous selection criteria utilized 18 articles researching cognitive reserve and revealed that high levels of cognitive reserve were connected to better cognitive performance measuring attention, processing speed, verbal fluency, verbal and spatial memory, and inhibitory control (Santangelo et al., 2019). Also, individuals with MS with higher cognitive reserve had more proficient working memory and appeared to be protected from deficits in long term memory (Sandry & Sumowski, 2014). From a neuropathology perspective, people with MS with higher premorbid verbal intelligence (taken as representing cognitive reserve), displayed preserved brain functional activity although there was strong evidence of grey matter atrophy. These individuals had more intact white matter connective tracts that were more similar to healthy controls than the MS participants with lower premorbid verbal intelligence (Fuchs et al., 2019).

Also included in the cognitive reserve indices are maximal lifetime brain volume (MBV), hippocampal volume and neuronal count (Sumowski & Leavitt, 2013; Schwartz et al., 2012). Brain reserve is different from cognitive reserve in that the former is based on the size and volume of the entire brain. A larger size of brain was found to moderately attenuate cognitive impairment, however brain reserve based on premorbid intellectual enrichment protected people with MS from MS related cognitive impairment separately from brain volume (Sumowski et al., 2013).

A lower level of education of 12 years or less revealed greater cognitive impairment in people with MS compared to those with a higher level of education, 12 years of education or more including some form of tertiary education (Rimkus et al., 2018). Two facets of cognitive

[2] Relapsing remitting multiple sclerosis: RRMS, secondary progressive multiple sclerosis: SPMS and primary progressive multiple sclerosis: PPMS

reserve have been proposed namely, passive which manifests in the form of IQ and educational attainment, and active reserve encompassing activities such as exercise, leisure activities and ongoing intellectually stimulating activities (Patel et al., 2018). High active reserve, which is a buffer for functional limitation over time seems to be more manifest in RRMS and appears to delay the onset of cognitive deterioration (Schwartz et al., 2013). Elevated active and passive reserve results are correlated with superior disease consequences, with higher levels of well-being and functional health, and are suggestive of the efficacy of rehabilitation measures (Schwartz et al., 2012). Functional reorganization takes place to compensate for deficits and adapt to brain changes particular in the early stages of MS when the brain is able to recruit reserved capacity (Jongens et al., 2012). However, the progression from a relapsing remitting course to a progressive course is thought to be the result of depletion of a person's cognitive reserve, the brain runs out of resources and the protective role of cognitive reserve dissipates (Portaccio, 2016).

Functional MRI studies have shown that even people with MS who test as cognitively intact show increased cerebral activation and wider neural recruitment in the cortex than healthy controls. Thus, increased recruitment of vital cortical networks may mitigate against the destructive effects on cognitive performance in tissue damage (Julian, 2011; Rocca et al., 2015). Maintained activity of the frontal lobe, as revealed by fMRI, is connected to improved cognitive functioning and by extension the association of brain atrophy and cognitive functioning is tempered by cognitive reserve (Rocca et al., 2014; Sumowski et al., 2009). However, increases in cortical recruitment are not indefinite as tissue damage escalates and so cognitive decline is inevitable. Thus, it appears as though cognitive reserve mostly attenuates the effects of regional rather than global atrophy on cognitive performance (Rocca et al., 2019).

Neuroplasticity in MS occurs at a cellular level with new sodium channels developing in demyelinated portions of the axons and ensuing synaptic changes. At a systemic level plasticity involves recruitment of parallel existing pathways or reorganization of various neurological sites (Filippi & Rocca, 2013). People with MS who are cognitively impaired show markedly lower recruitment of cognitively related areas compared with healthy controls and therefore, reveal lower cognitive reserve (Filippi et al., 2010). These authors also observed that in early MS an increased activation of the dorsolateral prefrontal cortex over one year was connected to improved processing speed and working memory. Some brain plasticity has been noted in patients with a lower degree of global atrophy when cognitive rehabilitation was initiated (Nocentini et al., 2014). Active cognitive reserve was observed more in relation to people with MS who have a lower symptom burden (Schwartz et al., 2013). The SDMT showed no change over time with people with MS who had 14 years and greater education attainment and higher premorbid IQ in comparison to individuals with less than 14 year of education (Benedict et al., 2011). Interestingly, in a study comparing RRMS with high educational achievement and controls, cognitive reserve did not seem to be a protective factor in terms of information processing speed, but was protective for additional cognitive spheres (Deloire et al, 2010). Higher education can also be protective against MS-related cognitive impairment and MS participants with low educational attainment performed more poorly on the higher speed version of the PASAT compared to education-matched healthy controls, whereas healthy controls with low educational attainment did not perform more poorly than highly educated healthy controls. MS participants with high educational attainment performed at the same level as educationally matched healthy controls (Scarpazza et al., 2013). The explanation provided by these researchers is that education is pursued when an individual is younger and the brain has greater plasticity, neural connections and efficiency and can thus,

cope better with pathology. For the purposes of the present research the Wechsler Test of Adult Reading (WTAR) and highest level of education provided insight into cognitive reserve and will be considered in relation to test scores.

The following section describes diagnostic parameters and the disease courses that MS takes.

Diagnosis of Multiple Sclerosis

The initial diagnosis of MS encompasses a neurological history and physical assessment. Clinical findings together with MRI data and other defined diagnostic methods, such as evoked-related potential tests and analysis of cerebrospinal fluid, are integrated in the diagnostic process.

Performing evoked-related potential (ERP) testing is a routine aspect of diagnostic practice and can reveal changes in the brain's electrical activity in reaction to a stimulus; auditory, visual or tactile. It is a non-invasive tool to evaluate brain functioning, by detecting abnormal CNS functioning, and helps define the site of clinically silent lesions. It gauges the speed of nerve conduction down sensory nerves to the brain by means of responsiveness to electrical stimulation and can detect the intactness of the axonal network (Habek et al. 2017; Jongens et a., 2012). The brain generates electrical current as a reaction to data received via the senses. This current is identified by means of electrodes which are adhered to the scalp. Even delays of 10 milliseconds suggest damage to neural pathways. ERP tests can be conducted using visual, auditory or skin stimulation. Analysis of cerebrospinal fluid is also used in MS diagnosis. It is the single most useful laboratory marker, as a feature of MS is the detection of oligoclonal bands which are prolific, compared to samples of cerebrospinal fluid in healthy people (Hartung et al., 2019). The results of ERP tests and markers of cerebrospinal

fluid are an important aspect of diagnosis and used in conjunction with MRI results provide robust evidence for a clinically definite diagnosis of MS.

Guidelines have been developed in order to create standardized diagnostic practice in MS. The diagnostic system that is most used and refined is referred to as the McDonald Criteria, first developed in 2001 by an extensive international panel (McDonald et al., 2001; Uitenhaag et al., 2005). The criteria are aimed at guiding clinical and diagnostic procedures towards a clinically decisive diagnosis. The key focus in the development of this diagnostic system was to objectively define dissemination (spread) of lesions in the CNS in both space and time and to streamline and standardize the diagnosis of MS. The McDonald criteria have subsequently been refined twice by Polman and colleagues (2005, 2011; see Appendix L for the McDonald table). In 2017, further revisions were suggested in consideration of new MRI advances in imaging and to strengthen the role of cerebrospinal fluid in diagnosing RRMS (Hartung et al., 2019; Thompson et al., 2018). Although the majority of the 2010 criteria have been maintained, the subsequent 2017 revisions have been implemented. The criteria were also expanded in part to accommodate symptoms experienced by people with clinically isolated syndrome. This system of diagnosis has more than doubled the rate of diagnosis of MS (Thompson et al., 2018; Zivadinov & Bakshi, 2005). The 2017 revisions facilitate an earlier and more accurate diagnosis of MS, which may in turn accelerate treatment with medication and rehabilitation measures. Additionally, the revisions address diagnosis in diverse geographical populations where differential diagnostic parameters should be considered. Research data supports the 2017 revisions and affirms that these expedite diagnosis without compromising diagnostic accuracy. The McDonald criteria have been studied and reveal a high sensitivity of 83% and specificity of 83% (Beesley et al., 2018).

To sustain the diagnosis of MS there must be evidence of two neurological exacerbations lasting at least 24 hours, one month apart, implicating different sites in the CNS. People with diagnosed MS have characteristic white matter lesions in 90% of cases (Olek, 2005). Exacerbations, sometimes referred to as relapses, result in inflammatory lesions, which may be observed in a number of physical symptoms such as, numbness and tingling, loss of motor function and visual disturbances. Magnetic resonance imaging findings can help confirm the diagnosis once these symptoms have been experienced. For example, if there is only evidence of a single clinical attack, MRI findings of two or more lesions can confirm the diagnosis (Polman et al., 2005; Polman et al., 2011). The first signs of demyelination reveal themselves as a clinically isolated syndrome. The symptoms may include optic neuritis, brain stem presentations and spinal cord pathology. The symptoms of clinically isolated syndrome may, therefore, be diverse and include double or impaired vision, numbness and tingling, limb weakness, balance problems, bladder and bowel irregularity, fatigue and cognitive impairment. As the disease progresses and the lesions and clinical symptoms become scattered in time and place, the diagnosis of clinically isolated syndrome gives way to that of MS (Feuillet, 2007; Thompson et al., 2018).

Multiple sclerosis can follow different disease courses. These courses are subtyped into relapsing remitting (RRMS), secondary progressive (SPMS) and primary progressive (PPMS; Denney et al., 2005; Papathanasious et al., 2014). Approximately 85% of people will follow an initial relapsing remitting course in which symptoms relapse and remit without disability necessarily progressing, although it typically will. For diagnostic purposes, the relapsing remitting course requires clear disease relapses with recovery after an attack. Commonly an attack may result in variable neurological complications, with visual disturbances, incoordination, limb paralysis or lameness. Those diagnosed with RRMS may have

neurological dysfunction lasting for days or weeks followed by nearly complete recovery (Heled et al., 2021). There may be residual deficiency afterwards, but the disease when diagnosed as relapsing remitting is not progressive. In sum, there are acute neurological episodes with substantial recovery and stability between episodes.

Of the RRMS group approximately 50% will develop into a secondary progressive course (SPMS) wherein remissions are minor and disability steadily progresses (Moccia et al., 2016). The disability is gradual and without recovery (Meyer-Moock et al., 2014). This represent a neurodegenerative stage of the disease as a result of axonal damage and neuronal loss (Demetriou, 2005; Bagnato et al., 2020). A smaller number of people, approximately10%, display a primary progressive course (PPMS) from initial presentation in which there is progressive disability from the first symptoms experienced and no relapsing remitting phase. There are very minor and temporary improvements, some plateauing, but there are no periods of obvious remission and neurological functioning progressively deteriorates (Miller & Leary, 2007). People with moderate to severe MS at initial assessment had increased disability across a 10-year period compared to people with mild MS. The disability entailed dysfunctions in mobility, cognitive processing and manual dexterity, and the mild MS group did not reach the disability of the more severe group over this period (Conradsson et al., 2018). Comparable results were observed in a 14-year longitudinal study of a group of people with MS who completed the SDMT every year. People with higher SDMT scores at baseline showed improvement in scores over time, while lower scores at baseline revealed worsening scores over time. Average scores remained at the average level. Since the SDMT is a test of processing speed poor functioning at baseline identifies the risk of cognitive impairment early on, which is likely to deteriorate further over time (Healy et al., 2021).

In MS, the most common presenting clinical symptoms are, sensory disturbance in the limbs (numbness, tingling, weakness), visual loss (optic neuritis, double vision called diplopia and impaired visual acuity), motor and gait disruption (balance), urinary dysfunction, fatigue and cognitive impairment (Olek, 2005). The disease courses are assessed according to the extent of disability, using the criteria on the Expanded Disability Status Scale (EDSS; Kurtzke, 1983), which was also used in the current study (Appendix A). This scale provides a degree of neurological disability in MS and it is used in neurological examinations to assess the extent of physical disability and functional deficits on an ordinal scale in increments of 0.5, ranging from 0 (normal neurological examination) to 10 (death due to MS). The greater the score, the more the dysfunction. Scores from 0 to 4.5 indicate people who are ambulatory and scores from 5.00 to 9.5 reveal progressive difficulty with ambulation. Generally, the range of scores for people with RRMS is from 0 to > 6.5 on the EDSS. However, this overlaps with the range of scores of people with secondary progressive MS, which may be from 4.00 to 9.5. The distinction in diagnosis is whether the disease is relapsing with recovery between attacks or is chronically progressive. The inclusion of people with RRMS in the present study was therefore not be based on EDSS scores, which were used for the initial screening, but on neurological diagnosis of the disease course made by a neurologist.

During the neurological examination eight functional systems are evaluated, namely pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, and other. Each is rated on a 0 – 5 or 0 – 6 scale on neurological examination. The EDSS is heavily weighted on physical parameters and is dependent on neurologists' assessments, which creates problems in reproducibility in research settings, as it does not contain robust psychometric properties. The scale's development predates the burgeoning literature of mood and cognitive impairment (Feinstein, 2007). Mood and cognitive dysfunction are significant symptoms and impairments

in MS, yet are excluded in this diagnostic measure (Amato et al., 2008). Subsequently, research now focuses on understanding the role of cognition and cognitive impairment as it develops in MS. There is another scale used to diagnose MS, which us outlined in the next section.

The Multiple Sclerosis Functional Composite (MSFC) was developed to reflect the importance of cognitive dysfunction as a diagnostic criterion. The National MS Society in the USA coordinated a task force of 16 international MS researchers who validated a multidimensional clinical outcome measure, the MSFC. The MSCF is an additional scale for measuring MS disability progression, and facilitates the assessment of three crucial components of MS namely, leg function and ambulation, arm/hand function and coordination, and lastly, cognitive function. These clinical measures were chosen as they are sensitive to current change, but also predictive of subsequent change due to MS progression. The composite consists of three tests, namely, the time to walk 25 feet in a straight line and back again to the starting point, a nine-hole peg test using dominant and non-dominant hands in separate trials (T25W) and the PASAT - 3 second (Fischer et al., 1999; Meyer-Moock et al., 2014). The MSFC is scored in a standardized way. A meta-analytic study reviewed the psychometric properties of the EDSS and MSCF, as both these scales are regarded as the most important measures used to evaluate and monitor MS disease progression. Both instruments we found to be valid and reliable, but also to have elements of clinical subjectively. Inter-rater reliability was greater for the MSFC, which appears to be more sensitive in detecting the progression of MS in the form of functional changes (Benedict et al., 2016; Bin Sawad et al., 2016). However, the scale used by the EDSS is better understood and more widely used in international research (Meyer-Moock et al., 2014). It is the measure that was used in the MS clinic where the present study was undertaken.

Early diagnosis of MS is crucial as treatment that is expedited can delay episodes and exacerbation of symptoms. Since cognitive impairment can be an early symptom of MS it was the focus of examination in the current study. Sensitive neuropsychological batteries and tests used in MS, such as, the MACFIMS, the SDMT and the Stroop are an adjunct to early diagnosis of cognitive impairment in MS.

Treatment of Multiple Sclerosis

Medication

The main intervention for MS is aimed at the immune response (Coggan et al., 2015). Immunotherapy medications are used to treat MS and can be divided into two groups. Corticosteroids which are used to reduce acute inflammation and stabilize the blood-brain barrier and secondly, disease modifying drugs, which are used in order to attenuate the demyelinating process to decrease the incidence and significance of relapse and reduce short-term disability (Kipp et al., 2015). There are over 20 disease-modifying drugs approved for the treatment of RRMS (Pappalardo et al., 2020). The drug deemed most efficacious by the neurologist is based on judgment and results of follow-up MRI results. There is compelling research providing evidence that these drugs reduce relapses, delay the progression of MS and the possible conversion to SPMS (Jongens et al., 2012). Treatment with a disease modifying drug can reduce the annual relapse rate by 29 % to 68% (McGinley et al., 2021). Researchers have also examined the results of using medication aimed at enhancing cognition. Studies of the use of Interferon beta-1b have revealed an encouraging effect on cognitive performance in speed of information processing, learning and memory (Chiaravalloti & DeLuca, 2008). Further research should to be undertaken to understand the impact these drugs have on cognition as the effects on physical functioning are significantly beneficial. Medication used in the treatment of dementia has also been used in MS with some success (Julian, 2011).

Rehabilitation

A metanalysis included 20 studies of rehabilitation in people with predominantly RRMS (Chen et al., 2021). There was some indication that neuropsychological rehabilitation actually decreased cognitive symptoms in MS. There are two approaches to cognitive rehabilitation. The first is restorative, aimed at reinforcing and strengthening extant cognitive skills through computer generated repetitive exercises. The second is compensatory rehabilitation to help compensate for difficulties by visualization or reminders (Chen et al., 2021). Cognitive training improved processing speed deficits, memory span, working memory, attention and verbal memory (Rosti-Otajärvi et al., 2014). Well-designed studies of cognitive rehabilitation are sparse in MS research and consensus for rehabilitation methods is lacking (Lamargue et al., 2020). People with MS with mild to moderate cognitive impairment were exposed to fifty 45-minute cognitive training sessions three times a week for four months. The program targeted the areas of information processing speed, executive functioning (inhibition and flexibility processes), working memory (central executive and storage capacity) and attention (selective, divided and sustained). The tasks were performed using different modalities such as, verbal, non-verbal, auditory, visual, oral, written and motor, with task difficulty that increased over time. The research was developed to address previous methodological flaws in rehabilitation research and was extensive and large in scope. Results revealed significant improvement on information processing speed scores, some increase in memory scores and in general daily functioning (Lamargue et al., 2020). Significant recovery in working memory, verbal memory, executive functioning and information processing speed have been found using a group-based cognitive rehabilitation program including three, one-hour training sessions per week over three months. The largest effect size was noted in information processing speed (Rilo et al., 2018). Cognitive improvement with cognitive rehabilitation interventions have been reported

in verbal and visual memory, learning, working memory, information processing, attention and executive functioning in RRMS (Brissart, Leroy et al., 2013). Concurrent greater effective neural activation in the dorso-lateral prefrontal cortex, which is directly involved with executive abilities, have been observed, suggested neuroplasticity based on training regimes (Chen et al., 2021; Mattioli et al., 2016). Cognitive rehabilitation also encouraged the participant's reflections and awareness of their cognitive deficits, which helped them develop compensatory strategies and thus, promoted self-agency and acceptance. This had a positive effect on quality of life (Klein et al., 2019). Cognitive rehabilitation depends on accurate and early detection of cognitive impairment from an early stage, especially as neural plasticity is a potential outcome.

Conclusion

Multiple sclerosis, the most common neurological disease of the CNS that is not traumatic in nature, is known as a young person's disease as most diagnoses are made from 20-40 years of age. Many physical aspects of life can be managed in RRMS, but cognition a vital factor of ongoing employment is significant impaired and within 10 years of diagnosis 50% - 80% of people with MS are unemployed (Julian et al., 2008). This in turn results in loss of self-esteem and life goals, and impacts social connections. Cognitive dysfunction is a primary, highly disabling symptom of MS with about 30% of people with MS who developed cognitive deficits after 3 years in contrast to only 6% who experienced physical deterioration and was detected very early in the disease process (Amato, Potaccio et al., 2010). As a demyelinating, inflammatory disorder, lesions and degeneration are seen in white matter nerve fibres, which impede or even block the conduction of nerve impulses. This results in a reduction of information processing speed leading to compromised functioning in cognition in a number of domains. Speed of information processing, attention and working memory are the

aspects of cognition regularly impacted in people with RRMS, with decrease in information processing speed a robust predictor of long-term cognitive deterioration. The aim of the present research was to ascertain subtle cognitive impairment as early as possible so that individuals have an awareness of cognitive difficulties and treatment can be expedited.

The expression of MS in individuals is highly variable and this chapter has provided an insight into the areas and structures of the brain that are affected. The reciprocal relationship between white and grey matter provides the background to the research question exploring the impact of auditory distraction on processing speed. Cognitively impaired individuals with MS have twice the number of lesions than those who were cognitively intact, with cognitive dysfunction related to the disconnection between brain areas cause by lesions to white matter fibre tracts. Damage to a diffuse network of white matter tracts reduces processing speed, which disrupts the communication network of grey matter. However, it is atrophy, resulting in brain volume loss, rather than lesion load that appears to cause most cognitive impairment. This is particularly observed in the thalamus, which is a hub and relays information to various parts of the brain. It is implicated in executive functions, which include attentional systems, inhibitory control and working memory. Since the thalamus is involved in selective attention, damage in this area can result in compromised attentional filtering, the subject of this research.

The next chapter will address in more detail the relationship of working memory, information processing speed and attention in MS. These particular cognitive domains are most commonly affected in RRMS and as such are the focus of the current research.

CHAPTER 3

MULTIPLE SCLEROSIS AND COGNITION: INFORMATION PROCESSING SPEED, WORKING MEMORY AND ATTENTION

Cognitive impairment is now thought to constitute one of the first symptoms of MS and can arise in the initial stages of the disease process. Overall cognitive impairment is rare as many cognitive features remain intact, however, there is a raised incidence of impairment in the cognitive domains that are impacted. In the early stages of RRMS, if cognitive impairment is established, it effects functioning in the workplace and in activities of daily life (Amato et al., 2010a; Benedict, DeLuca, Enzinger, et al., 2017; Campbell et al., 2017; Chiaravalloti & DeLuca, 2008; Deloire et al., 2010; Feinstein, 2007; Glanz et al., 2012; Heled et al., 2021; Mikula et al., 2017; Morrow et al., 2013; Nocentini et al., 2006; Ruet, Deloire, Hamel, et al., 2013; Strober, 2018; Sumowski et al., 2018). Early in the disease course it is important to identify and track any cognitive deficits and possible development of impairment, which will aid in treatment planning. This chapter details the cognitive domains that are impacted in RRMS and focuses on areas most relevant to the present research, namely, information processing speed, working memory and attention.

The intent of the current research was to broaden the limited theoretical and empirical framework underlying the impact of auditory distraction on cognition in MS. Although difficulty in selective attention due to distraction is acknowledged in MS, to date the present investigation is only the fifth study in the field spanning 25 years (Covey et al., 2016; Diamond et al, 1996; Diamond et al., 1997; Dittrich & Stahl, 2012; Patel et al., 2017; Randolph et al., 2017). The contribution of the present research to clinical application was to utilize a

distraction paradigm to refine two accessible and rapid tests, the SDMT and the Stroop. Auditory distractors were embedded in these tests, which are able to be used as part of a neurological assessment process and as an aspect of initial diagnosis. The SDMT and Stroop are regularly used in MS research and when relevant to the current goals, they have been highlighted in this chapter. The next chapter further explores selective attention and the mechanisms of distraction.

Multiple Sclerosis and Cognitive Impairment

Cognitive impairment is one of the earliest symptoms of MS and develops without a clear correlation to duration or extent of physical disability. It is increasingly recognized that cognitive dysfunction is pervasive, ranging from mild to significant in certain cognitive areas, and is one of the most disabling aspects of MS (Benedict, DeLuca & Enzinger, 2017). It impacts 45%-60% of people with MS and this prevalence rate has remained consistent across five decades of research (Julian, 2011). The etiology of cognitive impairment in MS is complex and multifactorial, as detailed in the previous chapter, involving white matter inflammation, demyelination and degeneration, white and grey matter damage (both focal and diffuse), pathology in certain cortical, subcortical and deep grey matter CNS structures, and includes cerebral atrophy and consequent ventricular volume expansion (Di Filippo et al., 2018). Impairment rates vary from up to 40% in relapsing-remitting MS (RRMS), to 60-70% in secondary progressive MS (SPMS; Di Filippo et al., 2018; Benedict, Bruce et al., 2006). The lifetime prevalence may be closer to 50-75% since cognitive dysfunction increases as the disease progresses. Severe dementia in the later stages of MS is apparent in 20-30% of cognitively impaired people with MS (Huijbregts et al., 2004).

Diagnosis in cognitive impairment is made when individuals experience changes in cognition and these are confirmed by neuropsychological testing. Cognitive deficits have

significant implications for all aspects of life, such as social and occupational functional impairment, psychosocial difficulties in self-esteem and maintaining relationships, problems with maintaining regular activities, losing a driver's license, poor reaction to therapeutic interventions, modest response to cognitive remediation, and increased susceptibility to psychiatric disorders (Benedict, DeLuca & Enzinger, 2017; Cox & Julian, 2005; Denney et al., 2008b; Heled et al., 2021; Morrow et al., 2010; Rao et al., 1991; Schultheis et al., 2001). Individuals with MS who develop cognitive impairments compared to those with only physical symptoms are less likely to be employed and less able to engage in activities of daily life (Borghi et al., 2013). Even mild cognitive impairment can lead to functional disability (Rogers & Panegyres, 2007). Early in MS cognitive changes are often negligible, which may be the result of the recruitment of other brain regions to compensate for injury before there is substantial degeneration (McNicholas et al., 2018).

Throughout the range of MS disease courses[3] cognitive abnormalities are evident. In some cases, impairment in cognitive functioning is detected without apparent physical symptoms and is ostensibly present when demyelination first occurs (Feinstein, 2004; Jongens et al., 2012; Schultz et al., 2006). In the initial presentation of MS even before a clinically definite diagnosis of MS is made, 20-30% of people with a clinically isolated syndrome present with cognitive difficulties. Regular deficits that develop include decrease in speed of information processing and diminished executive functioning, including selective attention (Summers, Fisniku et al., 2008; Summers, Swanton et al., 2008b). When cognitive impairment is detected in people with a clinically isolated syndrome, it is regarded as prodromal and is

[3] There are four courses of MS. Clinically isolated syndrome, which refers to symptoms only suggestive of MS, for example, optic neuritis or numbness and tingling in limbs indicate a first episode of inflammation or demyelination in nerve tissue, relapsing remitting MS (RRMS), secondary progressive MS (SPMS) and primary progressive MS (PPMS). From the first neurological symptoms noticed in clinically isolated syndrome, 85-90% of patients follow a relapsing remitting course within five years (Ron, 2018).

suggestive of conversion to clinically definite MS (Zipoli et al., 2010). However, if only one episode of symptoms has been detected, neuropsychological assessment detecting cognitive deficits strongly predicts, but cannot be used to diagnose early conversion to full MS (Zipoli et al., 2010).

Cognitive impairment is an early and prescient symptom of MS. In the early stages of clinically definite RRMS at the culmination of a three-year follow-up at least one third of RRMS participants had significant cognitive deterioration, while only six percent exhibited physical deterioration (Amato et al., 2010a). Nascent cognitive deficits tend to progress over time and once these occur, it is unlikely that they will significantly remit (Amato, Zipoli et al., 2006). Additionally, if cognitive deficits are apparent early in the development of RRMS, these tend to be associated with more widespread cognitive impairment later (Deloire et al., 2010).

There is evidence linking neuropathology to cognitive impairment, which can predict the future course of cognitive deficits (Summers & Swanton, 2008). Summers and Fisniku (2008) recruited 30 RRMS patients diagnosed within the three years prior to testing. MRIs and neuropsychological testing were performed at baseline and a year later. Five years later comparative neuropsychological tests were conducted on the RRMS group and results revealed significantly lower scores on memory, attention and speed of information processing. The rate of over-all atrophy in the first year of the study predicted deficits in cognition, particularly in decreased attention and speed of information processing and the rate of progression of neuroaxonal loss identified early in the disease was predictive of later cognitive impairment (Summers & Fisniku, 2008) .

With compromised cognitive performance so prevalent in MS there is a strong case for greater sensitivity in detecting cognitive impairment in the initial phases of MS, and some form of neuropsychological assessment should be part of a routine clinical examination (Borghi et

al., 2013; Guimaraes & Sa, 2012). Early detection of cognitive impairment also provides a baseline against which to monitor the rate of cognitive decline (Hoogs et al., 2010; Rogers & Panegyres, 2007). Additionally, the use of cognitive assessments can be an adjunct to MRI data in predicting the severity of deficits in individuals with MS. This is the key rationale for the current research and motivates the imperative to develop more sensitive, brief and administratively accessible assessment tools.

Importantly, general cognitive impairment is not reported in MS, instead specific domains such as, working memory, attention, information processing speed and executive functions are often more impacted than language ability and general intelligence (Adler & Lembach, 2015; Amato et al., 2008). People with MS have IQ scores that remain within the normal range and language functions are generally intact, but some subtle comprehension impairment is found (Feinstein 2004; Landon, 2011). There is substantial research revealing information processing efficiency and speed as the cognitive domain most frequently affected in MS (McNicholas et al., 2018). Decrease in speed of information processing affects a number of interconnected cognitive functions and the operation of higher cognitive mechanisms, for example, complex attention, executive functioning, working memory, as well as episodic, semantic, verbal and visuospatial memory are common cognitive deficits that emerge over time (Batista et al., 2012; Bergendal et al., 2007; Chiaravalloti & DeLuca, 2008; Costa et al. 2017; Genova et al., 2009; Julian, 2011; Rogers & Panegyres, 2007; Ruet & Brochet, 2013). With greater disease burden cognitive functioning decreases and a comparative study of people with RRMS showed deficits especially in information processing speed, attention and working memory, whereas individuals with progressive courses of MS exhibited extensive cognitive deficits not only in the domains already mentioned, but also executive functions and various

aspects of memory (Amato, Portaccio, Goretti, Zipoli & Hakik et al., 2010; Brissart, Morele et al., 2013; Ruet, Deloire & Charre-Morin et al., 2013).

The following sections examine the cognitive domains most affected in RRMS namely, information processing speed, working memory and attention, the interrelationship between them and the prevailing theoretical frameworks for each.

Information Processing

Introduction

In cognitive psychology, information processing refers to the manner in which the brain takes in information, organizes and stores it to be retrieved at a later stage. The flow of information involves perceptual systems, memory stores, decision-making processes and response mechanisms. The brain receives information via the senses and through focused attention information is retained in short-term memory for a brief period. Working memory has access to this information to address a targeted task and with the use of executive functions can retrieve information from long-term memory. Focal tasks are processed in this manner and new learning may then be encoded into long-term memory for storage. (APA Dictionary of Psychology, 2021). Thus, information processing theory focuses on the different cognitive mechanisms involved in perceiving, analyzing, manipulating, retrieving, learning and retaining information in memory stores in order to respond to various cognitive tasks. A comprehensive understanding of information processing involves theories of memory. These include the influential theories of Atkinson and Shiffrin (1968), Baddeley and Hitch (1974), and Cowan (1999), which will be detailed in the working memory section.

An additional critical aspect of information processing is speed. Therefore, information processing refers both to working memory which maintains and manipulates information for a brief period, and to the speed at which information is received, encoded and utilized. These

two operations are interconnected (Oreja-Guevara et al. 2019). In the MS population studies corroborate that working memory impairments are closely related to decrease in information processing speed (Chiaravalloti et al., 2013; Costa, et al., 2017; Kouvatsou, et al., 2020). Early in the RRMS disease process working memory is largely intact as are many cognitive functions, and when processing speed was statistically corrected people with MS were not significantly different from healthy controls in their performance on the Stroop and two tests of the DKEFS (Delis-Kaplan Executive Function System; Denney & Lynch, 2009). Similarly, Genova et al. (2013) observe that processing speed impairments were the main contributors to performance deficit on executive functioning tasks in people with MS. However, when time limits were imposed in simple and complex tasks of reaction time the RRMS group made significantly more errors (Parmenter, Shucard et al., 2007). Although, impaired processing speed accounts for deficits in working memory, the latter has also been acknowledged as a key area of difficulty in MS (DeLuca et al., 2004; Genova et al., 2012; Leavitt et al., 2011; Owens et al., 2013). The interconnection between these two functions of information processing have been extensively debated and two influential models have been developed by DeLuca et al. (2004) to elucidate the intricacy of the interface between information processing speed and working memory, namely the Relative Consequence Model and the Independent Consequence Model, which will be discussed in the next section.

Information Processing Speed

Efficient processing speed allows for understanding and then acting on external perceptual stimuli, higher level cognitive operations and output speed (Eizaguirre et al., 2018). Information processing speed is described as either the sum of time it takes to process certain defined information, thus time limits are not given, or how much information can be processed within a given time parameter (Chiaravalloti et al., 2013). The definition depends on where the

lens of research is placed. In the present study the first definition is the focus, as the SDMT and the Stroop test are measured by the amount of time necessary to finish the tests.

In real world situations efficient processing speed is necessary for optimal cognitive functioning, and deficits in processing speed pose significant challenges for people with MS competing in the employment market and completing activities of daily life (Pavisian et al., 2015). Information processing speed[4] is affected in 40-70% of individuals with MS and decreased information processing speed is noted as one of the initial and most ubiquitous of all cognitive difficulties (Chiaravalloti & DeLuca, 2008; Denney et al., 2005; Denney et al. 2008b; Hughes, Denney et al., 2013; van Geest, et al., 2018). Information processing speed impacted processes such as learning, memory, word retrieval and executive function as well as visual and auditory processing, and was a pivotal and primary underlying process for efficient performance of cognitive tasks (Drew et al., 2009; Eizaguirre et al., 2018; Langdon, 2011). There is compelling evidence that slowed processing speed in people with RRMS may be an early predictor of the rate of MS progression and that minor cognitive impairments in processing speed at initial diagnosis of MS strongly predicted long-term cognitive decline (Bergendahl et al., 2007; Lazeron et al., 2006; Moccia et al., 2016; Pitteri et al., 2017). From baseline, information processing speed declined precipitously when compared to other cognitive processes, and was independent of motor functioning. It impacted both simple tasks and those that involved a higher cognitive load (Olivares et al., 2005). Processing speed deficits also affected decision-making, and research revealed that RRMS patients made twice as many decision-making impairments as healthy controls (Muhlert et al., 2014).

[4] Processing speed is tested using a rapid serial processing format, primary by means of the PASAT, SDMT and Stroop test (Bodling et al., 2012; Hughes et al., 2011). This was the format used in the current study.

Longitudinal studies are essential in tracking the progression of information processing speed deficits and their impact on cognition. These studies provide further evidence that information processing speed tended to decrease as disease duration lengthened and that it was the most sensitive predictor of future cognitive capacity (Costa et al., 2017; Heled et al. 2021). In an eight-year longitudinal study of people with MS there was a substantial decline in speed of information processing over this time, which then was predictive of increased cognitive decline over the following 8-years. Verbal abilities and episodic memory were not affected. Notably, visual reaction time was significantly impacted compared to auditory reaction time. The reason for this disparity may be due to the optical tract which has an elevated vulnerability to MS lesions as it has a larger extension of length and volume compared to the auditory tract (Bergendal et al., 2007). Another longitudinal study over six years, revealed that people with RRMS exhibited a substantial debility in divided attention (dual task) and information processing speed on the SDMT, but this was not reflected in overall cognitive results (Hankomaki et al., 2014). At baseline the MS group had significantly decreased performance on attention and information processing tasks compared to a healthy control group. After six years the control group had fallen away and within group comparisons in the MS cohort revealed that information processing speed, which was tested by means of the SDMT, significantly declined. Additionally, measures targeting attention (sustained and divided) and information processing, memory, learning, reasoning and verbal functions[5] were assessed. The study did not include vocabulary tests or those of general knowledge or a test of reading such

[5] These tests took the form of subtraction tests (PASAT 2 and 3 second) the Weschler Memory Scale-Revised, the 7/24 spatial recall test for visual-spatial learning and recall, the Benton Visual Retention Test, verbal-visual construction reasoning, the Similarities and Block Design subtests of the WAIS-R, verbal functioning using two verbal fluency tasks, naming as many animal names as possible in 60 seconds and producing words with the letter S, as many as possible in 60 seconds.

as the WTAR (Weschler Test of Adult Reading), which may typically be given to measure premorbid cognitive abilities.

There are a number of theories that have been put forward to contextualize information processing speed in cognitive functioning in people with MS. As mentioned previously a central debate in information processing theory is whether it is the speed at which incoming information is processed, whether there is deficient processing in working memory or a combination of both that leads to deficits in task performance. In order to understand how this question is conceptualized in the MS literature, Costa and colleagues (2017) conducted a meta-analytic study which included 157 research articles investigating information processing speed in people with MS. Inclusion criteria specified that participants were 18 years of age and older, fluent in English, had a definite diagnosis of MS, methods and neuropsychological tests used to assess information processing speed should be clearly stated (the most frequently utilized test was the SDMT, n = 100, followed by the PASAT, n = 97 and then the Stroop Test, n = 23)[6], and should include a clear definition of information processing speed. The review findings illustrated the generally negative impact of deficits in information processing speed on working memory, executive functions, learning and memory. In the past decade, 12 different theoretical paradigms have been generated in an endeavour to define and theoretically conceptualize information processing speed in MS. Five have been most used in the MS literature, namely the Relative Consequence Model, the Independent Consequence Model, the Time Limited Mechanism, The Simultaneity Mechanism and the Neural Noise Hypothesis, which are briefly discussed below.

[6] Relevant to the present study the use of the SDMT to assess information processing speed has increased by 31% or more in the last eight years. Although the PASAT is widely used it is recognized as involving greater working memory resources than the SDMT, the latter which represents a more targeted test of information processing speed using relatively low working memory demands (Costa et al., 2017).

The Relative Consequence Model (DeLuca et al., 2004)

As the most commonly referenced model in MS, developed by DeLuca et al. (2004) it asserts that reduced information processing speed is the key cognitive impairment, which results in difficulties in other domains of cognitive processing including working memory. When processing speed deficits prevail to a critical level, functioning on assessments of working memory are affected. Information processing speed may decrease early in RRMS, but working memory impairment usually only becomes more apparent when the disease progresses in SPMS. According to this model as the disease course progresses from RRMS to SPMS deficient processing speed increasingly impacts working memory. In terms of the underlying neuropathology, lesions (areas of demyelination) in RRMS occur in white matter regions primarily in periventricular regions which affect processing speed. As MS progresses axonal degeneration and abnormalities in normal appearing white matter arise affecting more brain tissue and neural integrity, which increases deficits in processing speed, affecting other cognitive domains (Archibald & Fisk, 2000; DeLuca et al., 2004; Parmenter, Shucard et al., 2007). Processing speed deficits due to neurodegeneration have been noted in the literature on aging (Salthouse, 1996). This research may mimic some of the patterns of neurodegeneration in MS and is cited in MS studies, which will be discussed in the next section.

The Relative Consequence Model was tested in two studies using tests of rapid serial processing similar to the PASAT (Leavitt et al, 2011; Lengenfelder, 2006). In the first study, when additional time was given to participants to complete the tests, differences between their performance and that of controls was reduced or eliminated (Leavitt et al, 2011). In the second study the Tower of London Test, which assesses executive functioning particularly planning ability, was administered to MS participants under two conditions, timed and untimed. In the untimed condition people with MS achieved the same results as the control group. When time

restrictions were implemented the MS cohort scores were significantly poorer than the control group (Owens et al. (2013). These studies support the Relative Consequence Model, that information processing speed impairment underlies performance in other cognitive domains. However, this model is not universally endorsed as working memory impairments do emerge in RRMS, which then affect learning and executive functions. It is difficult to parse out the influence of information processing speed, which led to the development of the Independent Consequence Model (Berrigan et al, 2013; DeLuca et al. 2004; Parmenter, Shucard et al., 2007).

The Independent Consequence Model (DeLuca et al., 2004)

This model is based on the premise that cognitive deficits arise independently, depending on individual factors and are more related to specific areas of cerebral pathology rather than overall cerebral involvement. Thus, impairments in information processing speed and working memory may arise from different etiology. A possible reason for the different support of the two DeLuca models may be related to the diverse cognitive tests assessing speed of information processing that are selected in studies, which may confound results. The PASAT is widely utilized to assess information processing speed, but is a challenging test and relies not only speed of information processing, but on mathematical ability and significant working memory capacity (Tombaugh et al. 2006). Since these processes cannot be considered separately, poor performance is believed to be linked to impairments in processing speed, working memory or both (Anderson, 2012). The SDMT is becoming the test of choice as a rapid serial processing test, because it is easier to perform, instructions are understood quickly and it has a higher rate of completion by MS participants (Drake et al., 2010). The SDMT psychometric properties reveal higher sensitivity in detecting deficits in speed of information processing, since the cognitive load on working memory is significantly less compared to the PASAT and it is more reliable in test-retest trails (Lopez-Gongora, et al., 2015). Research

comparing the two DeLuca models supported the Relative Consequence Model after comparing results on the PASAT and SDMT (Anderson, 2012). The research highlighted the importance of choosing cognitive tasks that are as accurately as possible in separately testing the areas of information processing speed and working memory.

Deluca et al. (2004) and Costa et al. (2017) acknowledge the substantial contribution of Salthouse's (1996)[7] research on aging and the connection involving speed of information processing and interaction with higher level cognitive functioning. Salthouse (1996) purported that ageing is associated with decreased information processing speed, which leads to impairment in cognitive functioning. He describes two different processes, namely the Limited Time and Simultaneity Mechanisms, which are hypothesized as explanation for the connection between information processing speed and cognition.

The Limited Time Mechanism and Simultaneity Mechanism (Salthouse, 1996)

The basic premise of the theory of the Limited Time Mechanism[8] is that information processing is increased when processing speed is quicker and this frequently leads to higher levels of performance. When much of the available time is taken by earlier processing operations, the time required to perform later processing and task output is significantly restricted. This is especially pertinent when there are particular time constraints. Additionally, slower speed of cognitive processing ensues in a decreased amount of information that can be managed initially, resulting in loss of relevant information for later operations (Salthouse, 1996).

[7] This is research is based on deficits arising in information processing as the neurology of the brain changes with aging.
[8] Similar conceptualization to the Relative Consequence Model whereby speed of information processing is vital to task completion.

Salthouse (1996) also described the Simultaneity Mechanism which is founded on the premise that reduced speed of processing causes a decrease in the availability of information that is at a sufficiently significant level of activation to be used in cognitive processing. According to Salthouse, working memory enables the simultaneous processing of various elements of active information. The products of earlier processing, which must be held in working memory may be lost if processing is meaningfully reduced. Therefore, relevant information may not be accessible when it is required for vital process for example, encoding, searching, rehearsal, retrieval, integration or abstraction. In other words, information decreases in availability over time as it decays. Alternatively, the information becomes obsolete with rapidly changing cognitive demands. Even if the time allotment for cognitive processing is not limited, the internal restrictions of the various types of memory required for information processing entail a certain degree of speed. The ability to simultaneously process various pieces of information in working memory declines due to the aging process. In a similar manner, in people with MS slowed processing speed impairs encoding of information as suggested in the two mechanisms described above, creating a ripple effect of decreased learning and cognitive processing (DeLuca et al., 2004).

The Neural Noise Hypothesis (Kail, 1997)

This is the last of the five most commonly used theories of information processing speed that appear in the MS literature (Costa et al., 2017; Denney & Lynch, 2009; Kail, 1997). The premise is that information is conveyed by the CNS in variable amounts and strengths and takes place against a backdrop of neural activity or noise, which is the random variability of electrical impulse activity in neural networks. The faster information is processed the better it is able to penetrate the neural noise. If the speed of processing doesn't reach a necessary threshold then information processing is impaired. In MS, neural connectivity is disrupted due

to brain tissue injury resulting in diffuse, activated neural reactions. Reaction times of people with MS are generally slower than healthy controls. This is due to three CNS changes that occur as a result of the MS disease process (Kail 1997). First, demyelinating neurons convey information at reduced speed. Secondly, demyelination causes lesions or plaques which interrupt neural transmission and third, demyelinated axons deteriorate and cannot transmit information. In order to investigate this hypothesis Kail (1997) conducted a metanalysis of 12 reaction time studies comparing people with MS and healthy controls. Reaction times for the former group increased linearly compared to controls. Reaction times for people with significant symptoms of MS increased faster than the reaction times of those with less severe MS. Kail (1997) proposed that the increase in reaction times of individuals with MS compared to healthy controls mimics that of older adults compared to younger adults[9]. The reaction times of people with more severe MS approximate the values of 70-year old adults, contrasting with people with MS with less severe symptoms who had percentages similar to those for 55-year old adults. Thus, the Neural Noise hypothesis suggests that people with more significant MS symptomology process information slower than those with less severe symptoms. Neural activity is more diffuse as a result of axonal pathology and neural connectivity disruption, resulting in poorer performance. This hypothesis intersects with the role of distraction (especially auditory distraction), which is addressed in the next chapter.

These are all effective theoretical models for understanding information processing speed difficulties in MS and affirm that this is the key deficit in people with MS as it is essential for optimal cognitive functioning (Chiaravalloti et al., 2013; Costa et al., 2017; DeLuca et al.,

[9] Studies from aging literature examining neurodegeneration are used at times as means of comparison with MS neurodegeneration to understand the process of cognitive decline. The information processing theories of Salthouse are another example of how the conceptualization of information processing in MS is aided by the aging research theory.

2004; Genova et al., 2012; Kail, 1997; Kouvatsou et al., 2020). However, based on their metanalytic study, Costa et al. (2017) argue that these theories do not offer sufficient explanatory power for the mechanism of information processing speed. Consequently, they developed the Tri-factor Model, as an integrative paradigm.

The Tri-factor Model (Costa et al., 2017)

The unique contribution of this model is the premise that information processing is varied in complexity and the demand for processing in each particular task requires difference processing resources. Various tests are used to assess processing speed from simple reaction time tests to the SDMT and PASAT, which rely on more demanding cognitive constructs making it difficult to compare research results. This corroborates the argument that some tasks require working memory to a greater degree and are more complex (Anderson 2012). Comparisons of processing speed in different research protocols need to consider task difficulty and resultant cognitive load. There are two types of processing speed; simple which is the time needed for simple attentional tasks based on simple reaction time and concentration, and complex to process more cognitively demanding tasks, often utilizing working memory (Chiaravalloti et al., 2003). There is an intersection in cognitive tasks between simple and complex processing speed in that both types require vigilance, attention to stimuli, and speed of response. This in turn is reflected in studies utilizing assessments of both types of processing speed. They are not interchangeable and this type of construct contamination occurs when comparing tests that assess information processing speed (Costa et al., 2017). Importantly, people with RRMS manifest impaired processing speed in both simple and complex tasks compared to healthy controls. (Costa et al., 2017).

The Tri-factor Model of information processing speed proposes three phases of information processing from input to output, an expansion on the previous theories discussed

(DeLuca et al., 2004; Kail, 1997; Salthouse, 1996). The first phase entails cognitive speed functioning which refers to adequate speed to manipulate and plan an answer to complete a cognitive task within a given period. This stage relies on intact working memory if the information processing is complex. Additionally, information processing speed is not a single concept, but can divided onto simple and complex information processing tasks. Separate tests of simple and complex information processing can be compared to accurately assess the impact of both on information processing speed. Secondly, the model considers the transmission of sensory information, related to the functions of the visual and auditory systems. If either or both of these sensory functions are impaired, there is a preliminary delay in processing. This necessitates in all neurological assessments that vision and hearing are initially screened for potential deficits. Third, sufficient motor speed is required to provide a response. In later stages of MS, physical impairment will impede motor performance, but it is not a significant factor in RRMS. All three phases take place in quick succession. Each phase can be affected by brain pathology and all three need to be evaluated to properly assess information processing speed (Costa et al., 2017). Costa and colleagues (2017) note that the SDMT utilizes all three aspects of information processing. They reiterate that the SDMT is the most widely used test of processing speed in the MS cognitive literature and is strongly recommended for obtaining an initial baseline when assessing cognitive impairment in people with MS (Oreja-Guevara, et al., 2019). However, the SDMT is not able to separate out deficits in any one of the three phases in the Tri-factor Model. Further research is required to comprehend the contribution of each phase and the interaction between them, but psychometric testing can reveal the extent of impaired information processing.

Information Processing Speed and Multiple Sclerosis Neurobiology

The slowing of processing speed in MS is due to demyelination, resulting in network disconnection and decreased conduction speed (Lazeron et al., 2006). The functional neural network of the brain enables the flow of information during cognitive tasks, and as previously explored, this network is disrupted with MS related brain injury. There is a significant association between fibre tract damage and decreased information processing speed. Importantly, there is individual variability as a result of unique pathology displayed by people with MS (Bodling et al. 2012). Individuals with MS who exhibited optimal processing speed used fewer resources (less neural activation) than those with slower processing speeds (Silva et al. 2019). Similarly, a positive correlation was revealed between decreased brain functional connectivity and reduced information processing efficiency in people with RRMS, with total white matter lesion volume corresponding to disrupted functional connectivity (Soares et al., 2021). Once again, the most common and frequently used test in evaluating information processing speed neuropathology research is the SDMT, which has been used to assess functional, effective connectivity of the information processing speed network (Silva et al. 2019). White matter tract damage strongly predicted information processing deficits in people with RRMS as was indicated by poor performance on the SDMT (Eftekhari et al., 2017; Riccitelli et al., 2019). The performance of people with MS on the SDMT was associated with less activation in bilateral areas in the frontal and parietal regions in comparison to healthy controls. Participants with MS were scanned while performing the oral SDMT in order to evaluate functional connectivity patterns. This group was significantly slower, but as accurate as the healthy control group (Berrigan et al., 2014). Numerous neural connections were active in the MS group in the prefrontal cortices that were not observed in the healthy control group (Genova et al., 2009). Within both the hemispheres, the MS group utilized more frontal

connections to complete the task than the healthy control group, which indicated that greater neural recruitment was required to perform at a similar degree of accuracy as the control group (Leavitt et al., 2012). This pattern of activation is regarded as abnormal as greater neural recruitment is indicative of less efficient use of neural resources and is likely due to disease-related white matter damage resulting in cortical plasticity to maintain necessary functioning (Leavitt et al., 2012). This theory was investigated in a comparison between three groups; people with MS with impaired processing speed, those with MS exhibiting intact processing speed, and healthy controls. The first group had a brain connectivity pattern that differed from the latter two groups and suggested a disruption of top-down, conscious attentional control, which will be discussed further in the next chapter (Dobryakova et al., 2016).

In conclusion, researchers and practitioners aware of speed of information processing difficulties in people with MS removed restrictive time-limits in assessments in order to gauge cognitive capacity and under such circumstances people with MS were able to perform as accurately as healthy controls (Denney et al., 2008a, 2011, 2012; Lengenfelder et al., 2006; Parmenter, Shucard et al., 2007). In test situations, people with MS may achieve nearly the same results as healthy controls if given sufficient time to complete tasks, however this scenario does not mimic real-world challenges. Significant slowing of processing speed creates many difficulties for people with MS, as adequate processing speed is required to take in information from a number of sensory modalities, interpret and respond to it. The ability to process in an optimal manner allows for new learning, encoding and retrieval of information, timely responses and decision-making based on processing evidence at hand. Information processing implicates two main mechanisms, namely processing speed and working memory. The following section explores working memory, the interaction between this system and processing speed.

Working Memory

Slower processing speed impacts working memory, because less information is available for processing. Therefore, if less information enters working memory due to limitations in processing speed there will be difficulty in adequately completing a task. As noted earlier, a general deficit in information processing speed is noted in people with MS compared to healthy controls regardless of the level of complexity of a task (Denney et al., 2011; Hughes et al., 2011). It follows that a significant proportion of performance variance is attributed to processing speed and not working memory and numerous tasks that are believed to test working memory impairments in MS are actually more influenced by processing speed deficits (Genova et al., 2012; Hughes et al., 2011). In a working memory task (the Keeping Track Task) regression analyses revealed that in the MS group processing speed played a significant role in poorer performance compared to controls (Genova et al., 2012). However, according to the Independent Consequence Model (Deluca et al., 2004) working memory is affected in MS, particularly as the disease progresses and a number of theories have developed over time to understand this multifaceted construct.

Working memory is a complex operation involving sensory processing, short-term memory, learning and focused attention, with the capability to store information necessary for ongoing information processing (Chung et al., 2018; Oberauer, 2002). Importantly, working memory is short-term in that there are temporal memory limitations as well as capacity thresholds for processing (Beaman, 2004; Hughes, Hurlstone et al., 2013). It has been defined as an adaptive system that maintains and manipulates a limited amount of information that is pertinent to a task in a dynamic, comprehensive state for current cognitive functioning (Adams, et al., 2018; Cowan, 2017; Spillers et al., 2012). Researchers distinguish between circumstances in which information is stored and then repeated without processing or

manipulating it, which has been termed short-term memory, and those in which information is manipulated, termed working memory (Adams et al., 2018).

Although there are many conceptualizations of working memory, there are fundamental premises which are agreed upon. These are that working memory has limits on capacity, it functions in a separate manner from long-term memory and contains information processing mechanisms such as, rehearsal to prevent decay and the ability to retrieve necessary items from memory storage (Adams, et al., 2018). However, there is an ongoing debate in the literature concerning the theoretical conceptualization of working memory. One view posits a modular system involving separate resources devoted to the storage and processing of information mainly in auditory and visual modalities. To accomplish this, distinct parts of the cognitive system are utilized to initially process these perceptual modalities before a focal task can be accomplished (Atkinson & Shiffrin, 1968; Baddeley 1992, 2000, 2003, 2012; Baddeley & Hitch, 1974, 2019). The other view is that distinct modalities are not required to process initial stimuli, but rather the focus is on shared attentional resources, that have limited capacity (Cowan, 1999, 2008, 2017; Oberauer, 2002, 2019; Rhodes et al, 2019). These two broad approaches, with the major theoretical advocates, will be examined in the next section.

The Multi-Store Model (Atkinson & Shiffrin, 1968)

One of the first models of memory was developed by Atkinson and Shiffrin (1968), and is known as the Multi-Store model or Modal model. Their model provides a comprehensive theory of information storage and has three components or stages. The first is the sensory register or store, whereby sensory information enters memory[10]. Sensory memory only lasts for up to three seconds and the role of the sensory register, comprised of sensory buffers, is to permit information to be transferred to short-term memory. Processing does not

[10] There are multiple registers with a different sensory receptor for each sensory stimulus.

occur in sensory memory, which filters out information deemed irrelevant and only sends what is relevant to the second stage, the short-term store. The transferral of information to short-term storage can only occur when attention is provided to a sensory event, otherwise it rapidly decays. During the second stage, once information reaches short-term memory for use in working memory[11], further filtering occurs through rehearsal maintenance and storage occurs for approximately 20 to 30 seconds. Working memory has limited capacity and only a certain number of pieces of information can be processed at a time[12]. Within this short-term store information does not have to match the same sensory modality as the input, for example, information received such as written text can be held as auditory memory and auditory input can be visualized. Various methods are used to store information such as repetition, connecting information, relating information to meaningful experience or breaking up information into chunks (Vinney, 2021). Cognitive load capacity varies from person to person as does an individual's ability to focus attention. Task difficulty is also an important aspect of processing capacity. The third stage in the Multi-store model is the long-term store, which is limitless and it is the location where information is stored more permanently. The longer an item is held in short-term memory, the stronger the retention in long-term memory is likely to be. Retrieval from long-term memory involves a network of associations, so that latent information can be activated to correspond to the requirements of task output (Atkinson & Shiffrin, 1968).

The concept of the unitary short-term store set up the theoretical basis for the working memory model of Baddeley and Hitch (1974). They developed the concept of working memory

[11] The Multi-store Model conceptualization of short-term memory is akin to the concept of working memory
[12] According to Miller (1994 based on his earlier work in 1956) the number is 7 plus or minus 2. Although Cowan (2015) maintains that this number is debateable and closer to 4 chunks of information. This issue is discussed later in the chapter.

to contain not only storage, but the active manipulation of stored information for information processing (Barrouillet et al., 2011).

The Multicomponent Model (Baddeley & Hitch, 1974)

Baddeley and Hitch (1974) argued that the short-term memory described in the Multi-Store model (Atkinson & Shiffrin, 1968) was too simplistic and linear, since the limited amount of information held in the short-term store does not sufficiently account for more complex information processing nor guarantee transfer to long-term memory. Whereas short-term memory can contain information, working memory as a multicomponent system can retain and then process information from different sensory modalities. Thus, working memory is viewed as a complex interactive system that mediates between cognition and action, and manages information from various sensory modalities during different stages of processing (Baddeley, 2012). "The concept of working memory proposes that a dedicated system maintains and stores information in the short term, and that this system underlies human thought processes" (Baddeley, 2003, p. 829)[13]. Importantly, a central principle of working memory is that capacity is substantially limited as there are a set number of memory slots, which only allow a limited number of items to be encoded at any one time (Baddeley, 2003; Endress & Szabo, 2017).

Baddeley and Hitch (1974) initially conceptualized working memory as a three-component model of short-term memory[14] with limited memory and attention capacity. They further developed the constructs of sensory memory and short-term memory, by introducing the phonological loop, visuospatial sketchpad, and the facilitating role of the central executive

[13] Baddeley and Hitch (1974) continued to develop their theory for over 40 years and they regard it as providing a theoretical construct to account for how memory and attention combine to enable complex cognitive processes.

[14] Expanding the Atkinson and Shiffrin (1968) model of short-term memory

in information processing, as components of a complex and dynamic working memory model (Baddeley, 2012). The central executive system made up of an attentional control system, actively coordinates and directs information processing by means of two 'slave' or store systems, the phonological loop (verbal and acoustic content) and the visuospatial sketchpad (visuo-spatially presented information), which function passively in regard to processing (Baddeley, 1992). Passive storage refers to information stored for a limited time. Active storage occurs when material is manipulated or transformed, and this process has greater complexity requiring executive functions (Vecchi et al., 2005). Passive stores are accompanied by active processes such as, rehearsal of incoming information to prevent deterioration of information. Baddeley (1992) further refined the model by exploring the role of attention in filtering incoming information that is then maintained internally by means of working memory. The functions of attention were specified as including focused, divided, switching between tasks and the capacity to interface with long-term memory.

The Central Executive

The central executive is the controlling, supervisory centre of cognitive processing, whereby information processes are regulated through various memory stores, which encode incoming information and retrieve information necessary to a cognitive task from long-term storage (Baddeley, 1992, 2000, 2003, 2012; Baddeley & Hitch 1974, 2019). Incoming information is received through the two subsystems, the phonological loop, which keeps auditory information for a short time with an articulatory rehearsal procedure to prevent decay, and the visuo-spatial sketchpad, which holds visual and spatial information also used for rehearsal for longer storage. The fourth storage element of the storage system is the episodic buffer that integrates information stored within the subsystems and allows the flow and transmission of information between perception, short-term and long-term memory (Baddeley,

2000). A vital aspect of the central executive is the allocation of attention in the form of selective attention, inhibition and shifting between tasks to the two short-term subsystems systems when required, and the planning of future cognitive activities for problem solving (Chung et al, 2018; Spillers et al., 2012).

The central executive draws on the work of Norman and Shallice (1986) who proposed that attention controls action by means of two separate paths. The one is based on well-learned habits or schema which require little attentional control. Schemata are actuated by sensory stimuli, which are then performed automatically through a learning a pattern of input-output rules. However, in order to assist goal-directed, non-routine behaviour and override habitual responses the second process, the Supervisory Attentional System, becomes activated in pursuit of higher-level cognitive goals. It provides executive management of the subsystems of information processing through top-down control, which occurs through deactivation of automatic schema (Cieslik et al., 2015). The concepts of top-down and bottom-up attention are explored in depth in the section on attention.

The Phonological Loop and Visuo-Spatial Sketchpad

The phonological loop is a temporary store, a short-term memory trace, which holds information for a few seconds before it fades or decays, and is refreshed by two possible foundational verbal procedures, one articulatory and the other auditory. These are designated as the ‘inner voice’ and the ‘inner ear’. Articulatory rehearsal, also known as subvocal articulation, is required for the refreshing of information so that it remains in short-term storage (the phonological store) and may also be conceived of as an internal speech-based code (Baddeley & Hitch, 2019). The phonological loop also depends on the phonological and lexical representations within long-term memory and language that are procedurally based for rehearsal (Baddeley, 2012).

The visuo-spatial sketchpad allows the creation of a mental image, the ‘inner eye or inner scribe’ of information that can be manipulated before it is refreshed and fades (Logie, 2011). This information takes the form of images in terms of shape, colour and spatial location. Refreshing of visuo-spatial material appears to be maintained by a continued focus of attention on the target information. There is substantially more research in the linguistic semantics area than in the visuo-spatial sphere so much theory is conceptual in the latter rather than empirically based, as in the former.

The Episodic Buffer

A fourth subsystem, the episodic buffer, was developed to hold multidimensional stimuli. It integrates and binds information in working memory (Baddeley, 2000). The episodic buffer as a transitional storage system, is able to assimilate and integrate perceptual information and provide the other subsystems of working memory with relevant information from long-term storage. It is limited though, with capacity of about four chunks of information. Much information processing occurs at a process level with combined processes realized within the episodic buffer. Thus, retrieval from the buffer occurs through conscious awareness. It forms a link between the perceptual bottom-up approach and the top-down approach of the executive and attentional aspects of working memory. It is the central executive that controls access to the buffer. Within the episodic buffer, verbal tasks interface with verbal perceptions and do not include visual short-term memory nor visual tasks. The latter interface with only visual perception held in visual short-term memory and not verbal short-term memory. Thus, the distinct buffers control distinct modalities of information (Baddeley & Hitch, 2019). The perceptual buffers feed into short-term storage, hold information for manipulation allowing for transfer to long-term store. (Spiller et al., 2012). The episodic buffer has capacity for passive storage distinct from the central executive, whose function is purely attentional and active. The

model (Figure 3.1) is presented as a "theoretical framework offering a coherent account of how memory and attention combine to facilitate complex cognition" (Baddeley & Hitch, 2019, p. 102).

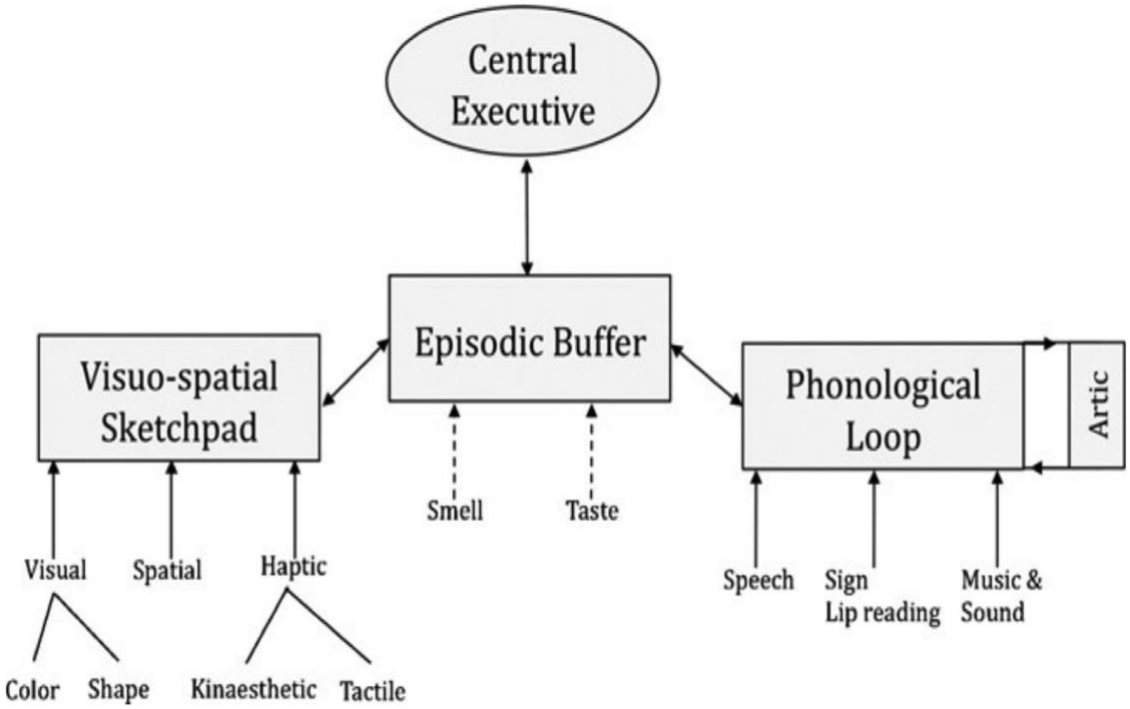


Figure 3.1

The Multicomponent Model of Working Memory. (Baddeley & Hitch, 2019, The phonological loop as a buffer store: an update. Cortex,112, p. 101. Copyright Elsevier Ltd[15]).

Latterly, Baddeley and Hitch (2019) further defined the difference between short term-memory and long-term memory. Previously developed structures within long-term memory enhance working memory. Memory is separated into two classifications, archival in which

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information is stored over a long period and shorter-term buffer storage. Buffer stores allow the organization of two streams of information that might be different in format, for example speed of input or content.

A major criticism of the Multicomponent model (1974) is that the relationship between storage and processing in working memory, and the role that attentional resources within the central executive play are not adequately established (Barrouillet et al., 2011). The two following theories, the Time-Based Resource-Sharing model (TBRS) Model (Barrouillet et al., 2011) and Embedded-Process model (Cowan (2008), expand on the nature of these functions in working memory.

The Time-Based Resource-Sharing Model (TBRS Model; Barrouillet et al., 2011)

Barrouillet et al. (2011) maintains that there is a balance between the extent of information that can be retained actively in working memory and the cognitive load engaged in simultaneous processing. They propose that storage and processing in working memory are not separate, but both require the same cognitive function namely, attention. According to the Multicomponent model (1974), when attention is essential for processing a task it is not accessible for the maintenance of information for memory. Thus, these elements decay and there is memory loss when attention is switched to processing. Any increase in cognitive load results in memory loss. There is then a fractionation between memory storage and processing. As cognitive load increases, the refreshing process becomes shorter and may be incomplete (Barrouillet, et al., 2011; Cowan, 2014).

The TRBS (2011) model proposes time-based sharing between memory storage and processing, whereby attentional resources are shared depending on the demand of the particular function. Executive attention shifts between rebuilding decaying memory traces and processing information. A novel aspect of this model is that articulatory rehearsal in the

phonological loop, used to encode incoming stimuli in short-term storage, is separate from attentional refreshing allowing for greater processing under cognitive load (Glavan & Houpt, 2019). According to the TRBS model (2011) attentional refreshing operates on retrieval from declarative memory in long-term storage, while the phonological loop continues to reactivate memory traces. These memory traces can then be used for a cognitive task together with items from the articulatory rehearsal loop. Thus, articulatory rehearsal is a signal to guide attentional refreshing. Cowan (1999) elaborated on the mechanism of retrieval from long-term memory by means of executive attention and attention automatically activated by incoming stimuli in his Embedded-Processes model.

Embedded-Processes Model (Cowan, 2008)

According to Cowan (2008) the pivotal role of attention to the allocation of processing resources was underdeveloped in the Multicomponent Model (1974) of working memory. The unique approach of Cowan's (1988) theoretical model of information processing maintains that there are two characteristics of working memory. The first is the activated component of long-term memory, which becomes galvanized when processing specific tasks. Second, attention is focused on incoming stimuli and allows for an object or concept to be bound together with activated items from long-term memory to form novel concepts and integrate new learning. Attention is a central feature in both processes. These processes are embedded or fixed cognitive organizations within working memory and this conceptualization led to the formulations of the Embedded-Processes model (Cowan, 1999). This model involves five principles that highlight the connection between memory and attention. First, working memory material arises from a set of relevant long-term memory content, that is currently stimulated to be used in a task for the present focus of attention. Second, the focus of attention has limitations in capacity as well as time-limits. There is a time-limit in stimulated memory with items

decaying after 10-20 seconds unless there is reactivation. There has been controversy related to the item capacity limits in working memory. In 1956 Miller hypothesized that the upper limit of information processing was in the region of seven items (+ or - 2) of information. The number of pieces of information can be increased by recoding or using various mnemonics, such as chunking, which allows more information to be processed (Miller, 1994). Rather than seven chunks as Miller (1956) stated, Cowan (2015) suggested that there are three to five chunks which can each contain more than one item (Cowan, 2015). The third principle of the Embedded-Processes model (1999) is that attention is mediated by both voluntary (a central executive system) and involuntary mechanisms such as an attentional orienting system. Thus, attention is directed outward towards stimuli (which may include distractor material) or inward towards long-term memory containing activated material as well as information that can be consciously retrieved through cues. The fourth principle, is that an individual will habituate to stimuli that are unchanged over time and these will not require an orienting response. Fifth, conscious awareness can influence processing allowing a search in memory for relevant information. Information in present focus is promptly available to working memory, but information can consciously be activated for retrieval. As mentioned, an essential aspect of attention is that it can be directed outward towards stimuli or inward towards long-term memory. Saliency will result in automatic directing of attention to the stimulus or attention may be voluntary directed by the central executive (Cowan, 2008)[16].

According to this model, working memory is made up of activation, information to which attention and awareness is directed, and long-term memory. The regulation of working memory occurs as result of the central executive controlling the focus of attention. This control

[16] The topics of automatic attention and stimuli saliency (bottom-up) and consciously directed attention (top-down) are extensively addressed in the section on selective attention and the next chapter as they are foundational for this study.

also provides activation of information in memory. Short-term storage mechanisms are also contained within working memory, however Baddeley and Hitch (1994) were more successful in integrating these mechanisms into their theory. In terms of encoding incoming information, Cowan (2008) refers to multiple coding modalities rather than specific modalities such as the phonological loop or visuospatial sketch pad of the Multicomponent Model (1974). The Embedded Processes model (1999) does not separate the phonological and visuospatial stores, rather all new information input can become the focus of attention and activate long-term memory (Adams et al., 2018). Cowan (2008) acknowledges that research into working memory has overwhelmingly been dominated by the influential work of Baddeley, Hitch and colleagues both in research output and theoretical development (Cowan 2017).

The Multicomponent model (Baddeley & Hitch, 1974), modified by Baddeley (2000) is an example of the use of a theoretical model for studying working memory in people with MS (Kouvatsou et al., 2022). Results indicate that breaking down working memory into components provides a more complex understanding of impairment in people with MS. Thirty-eight people with MS and 27 matched healthy controls were tested using 12 cognitive tasks, covering the four components of the Multicomponent model (Baddeley & Hitch; Baddeley, 2000) namely, the phonological loop, the visuospatial sketchpad, the episodic buffer and central executive. The tests covered the domains of verbal short-term memory, visual and spatial short-term memory, backward digital and block recall, to test central executive functions, and included memory and learning tests to assess the episodic buffer aspect of working memory (Kouvatsou et al., 2022). The episodic buffer, which assimilates information across working memory elements and long-term memory was significantly impaired compared to deficits in the phonological loop, central executive and spatial component of the visuospatial sketchpad. There was no dysfunction in the visual component. Greater deficits were found in

the process of storing information rather than the active processing of this information (Kouvatsou et al., 2022). The following section provides further details of the interface of working memory and MS.

Working Memory and Multiple Sclerosis

Working memory is impaired in people with MS compared to healthy controls. The former have difficulty completing two tasks simultaneously and manipulating stored information (Kouvatsou et al., 2020, 2022; Lengenfelder et al., 2006). Significant deficits in attention and vigilance, also impact working memory functioning (Langdon, 2011). As established previously, speed rather than accuracy is the essential information processing difficulty in people with MS even when cognitive load is low (Lengenfelder et al., 2006). When cognitive load on working memory is high, there is a further decrease in processing speed in people with MS and as the disease progresses, higher cognitive load results in impairment in both speed of information processing and working memory (Farez et al., 2014).

There are three possible hypotheses for the differences in processing speed and working memory in people with MS (Lengenfelder et al., 2006). Two theoretical models were discussed which attempt to conceptualize the relationship between working memory and information processing speed. The Relative Consequence Model (DeLuca et al., 2004) maintains that the primary problem in cognitive processes lies in processing speed and this results in deficits in other cognitive domains, an example being working memory; thus, impairment in working memory is secondary (Chiarovalotti et al., 2013; Costa et al., 2017; DeLuca et al., 2004). The Relative Consequence Model (2004) was challenged by Berrigan et al. (2013) who argue that even in RRMS from the earliest stage working memory is impacted separately from reduced processing speed. However, Deluca et al. (2004), in their Independent Consequent Model proposed that impairment in processing speed may be independent and co-occur with deficits

in working memory, thus, working memory and information processing deficits develop separately with each affecting information encoding (Archibald & Fisk, 2000; Berrigan et al., 2013). This idea was initially developed by Archibald and Fisk (2000), who suggested that as MS progresses not only does processing speed decrease, but working memory capacity becomes limited and leads to difficulties in learning new information. The best explanation may include both premises, since processing speed and working memory do not function in isolation in real world settings (DeLuca et al., 2004). There is substantive research associating white matter microstructural tissue with working memory functioning and it was established in the previous chapter that in people with MS white matter microstructural brain injury is revealed in DTI and is associated with cognitive dysfunction (Genova et al., 2013; Chung et al., 2018; Hoogs et al., 2010; Llufriu et al., 2012; Santiago et al., 2007). Importantly, speed of processing is a more sensitive measure of the processing of information in people with MS than is working memory.

The third possible explanation for the differences between processing speed and working memory performance in people with MS involves the concept of cognitive reserve. When task difficulty increases greater cognitive reserves are recruited. Cognitively impaired individuals with MS utilize more available resources earlier than cognitively intact people with MS and under high cognitive load performance on working memory tasks decline (Lengenfelder, 2006).

Performance is significantly worse on tasks that necessitate manipulation of information speed in working memory in people with MS when compared to controls (Chiaravalloti et al., 2013). These tasks place a greater cognitive load on working memory. To assess this premise, people with RRMS who were cognitively intact (as assessed on the MACFIMS) were given a task-switching protocol. This protocol involved alternating trials of

different tasks using different executive processes. There were two tasks; the first required participants to discriminate numbers as odd or even and in the second task, they were required to determine whether a number was greater or less than the number 5. Answers were provided with either the left index finger (odd number and less than 5) or right index finger (even number and greater than 5) on a computer keyboard. Compared to a matched control group the RRMS group were significantly impaired in shifting between different tasks, revealing deficits in working memory and executive control (Migliore et al., 2018). As the MS disease burden increases, cognitive reserve declines and cognitive capacity becomes overloaded leading to working memory impairment. Thus, evidence suggests that the functions of information processing speed and working memory work in tandem and are in turn interrelated with attention.

Attention and Working Memory

Working memory was explored in this research from the perspective of the Multi-Store model (Atkinson & Schiffrin, 1968), which proposes that sensory stimuli from the external environment are processed by means of sensory registers for a brief period of two to three seconds. If attention is given to the sensory event, it enters into short-term memory or store for processing and may then be transferred to long-term memory. Transfer to longer short-term memory or long-term memory is by means of rehearsal, repetition, and/or encoding. Conscious attentional controls are used in this process. Building on this, the Baddeley and Hitch (1974, 2019) and Baddeley (1992, 2003, 2012) Multicomponent model hypothesizes a dynamic structure of working memory which facilitates the processing of information from different sensory modalities into sensory memory, which then connects to short-term memory. The controlling component of working memory is the central executive, which through focused, divided, and selective attentional modes processes information aided by the episodic buffer

interfacing with multi-modal short-term memory components and long-term memory. The role of attention was not fully developed in this model. However, Cowan's (1999, 2008, 2017) Embedded-Processes model developed the role of attention more fully. This model views long-term memory activation as pivotal in working memory processing. Attention is necessary for activation and the interfacing of the different aspects of memory. There is a necessary divide of attentional resources between incoming stimuli and processing this information via memory storage, a vital component of which is the retrieval of pertinent information for a target task from long-term memory (Cohen, 2014). Further, the Time-Based Resource-Sharing model (Barrouillet et al., 2011) maintains that there is an accommodation between information actively retained in working memory and complexity of a task or cognitive load, necessitating an attentional shift. This transferring of attentional focus in working memory is explored in the following section.

Working memory is conceived of being the interface between external perceptions (usually visual and auditory), which attentional processes select to actively maintain for cognitive processing (Chun, 2011; Chun et al, 2011; McGabe et al., 2010). Although the contents of attention and working memory often overlap the relationship is not fully understood (Fougnie 2008). They are theoretically distinguishable processes, however, practically they are highly interactive (Kollndorfer et al., 2013). Oberauer (2019) in his review paper reiterates that working memory and attention are closely linked.

There is greater agreement, however, in terms of the manner in which working memory is defined compared to attention. Attention is understood as a limited resource for information processing within working memory and also, by extension as a mechanism for the selection of information for immediate processing when an item in working memory automatically captures attention (Cowan 1999). Specifically, selective and sustained attention are essential

to working memory to aid in speed of information processing and retention of information necessary for the completion of current tasks (Awh et al., 2006). These attentional processes are active aspects of working memory to sift and discriminate information (Wickens, 2021).

A key distinguishing feature of working memory is its limited capacity. This limitation is related to interference in the form of many competing stimuli, which need attentional sifting resources for processing and the ability to effectively deal with this load. When more items are active in working memory, interference becomes stronger as capacity is stretched. Conversely, if interference in attention is low, working memory capacity is increased. Attentional systems are therefore required to counteract or inhibit interference (Dalton et al., 2009; Konstantininou et al., 2014).

Oberauer (2019) expanded on the importance of the source of information for processing and postulated that attention may be distinguished along two dimensions. In the first, information is gained by attending to current perceptions in the environment and also, includes attention to remembered events and content not currently perceived. The second dimension involves attending to cognitive goals and the mental processes that are required to meet these goals. Attention allows the selection of stimuli to be encoded into working memory, which is filtered according to our intentions, and long-term-memory information that is retrieved only if it is relevant to a current task. Additionally, attention is controlled when it is directed towards current goals (top-down), but is automatic when it is influenced by sensory information not pertinent to the current goal (bottom-up). Thus, attention involves the processing and selection of material to the exclusion of other information. Three attentional brain networks exist, namely alerting, orientating and executive attention, which will be explored in the next chapter. In addition to the complexity in describing the multifactorial concept of attention, working memory itself has many components, further complicating

attempts at understanding their role in information processing. Some independence occurs between attention and working memory regarding simple visuospatial attention, but when executive attention is required, there is overlap between the two cognitive processes (McCabe et al., 2010; Fougnie 2008). Selective attention enables the efficient processing of new information at all stages of processing and plays the role of a 'gatekeeper' to actively regulate, manipulate and update those items, which will use the limited space in working memory (Awh et al. 2006).

Conversely, working memory maintains content to guide selective attention. In this sense, working memory and attention could be conceptualized as one system with attention being directed internally as working memory or targeted externally as selective attention (Kiyonaga & Egner, 2014). The relationship between these processes is reciprocal in that the domains overlap to the extent that differentiation becomes difficult to define. Aligned with this conceptualization, Oberauer (2019) proposes that attention selects and prioritizes representations for use in working memory, that working memory is a function of attention and the two functions cannot be considered separately. Working memory and attention are clearly close and intertwined, and their connection is foundational for information processing, the latter which requires sufficient speed for optimal working memory function.

Attention and Processing Speed

Working memory is the mechanism for maintaining and manipulating information most currently needed, for a short period, for processing an ongoing cognitive task (Baddeley, 2012; Wickens & McCarley, 2019). There are short-term storage mechanisms, in addition to attentional control processes to control the movement of information in and out of short-term memory. Thus, information is retained in short-term memory while information processing that is needed to solve current problems is able to operate. The process is aided by high working

memory capacity, which correlates with the capacity to focus attention. Decreased processing speed seems to be one of the major underlying features of cognitive dysfunction in MS even in the initial phases of RRMS and underlies other cognitive dysfunctions such as impairment in working memory, attention, executive deficits and difficulties in acquiring new learning (Genova, Hillary et al., 2009; Ruet et al., 2013). There is considerable evidence of deterioration in attention and information processing speed in people with MS at an early stage of disease development, as well as evidence that these functions are interrelated and work in tandem (Deloire et al., 2006; Genova, Hillary et al., 2009; Olivares et al., 2005). It follows that the connection between attention and processing speed is vital, in that the ability to remain attentive to particular tasks requires selective and sustained attention and efficient processing speed so that information is not lost in working memory. In support of this, research involving a 6-year follow-up of people with RRMS documented a substantial decrease in divided attention and information processing speed, whereas additional cognitive measures, for example, memory, reasoning, verbal and psychomotor performance did not change. The cognitive functions of divided attention and information processing speed were the first to show decline over time (Damasceno Et al., 2020; Hankomaki et al., 2014). Additionally, people with RRMS revealed delayed responses and difficulties in attention as inhibitory controls were mobilized when competing stimuli were presented. These inhibitory controls led to delays in timely responses in people with RRMS (Wojtowicz et al., 2013). This in turn resulted in impairment of higher cognitive mediated attentional control pointing to attentional network deficits in MS (Crivelli et al, 2012; Urbanek, 2010; Wojtowicz et al., 2013). When studying information processing speed and attention in MS, deficits in processing speed were more pronounced than deficits in attention, and when speed of information processing was

controlled the variances were found in the brain's alerting network that maintains a state of vigilance (Roth et al., 2015).

Attention

The present research aimed to elucidating the impact of auditory distraction on selective attention, and the effect this potentially had on information processing speed. An understanding of the components of attention is therefore necessary. We are surrounded by information, which enters our cognitive landscape via the senses, various aspects of which are chosen to be attended to. For survival reasons, the human brain is primed to be alert to environmental stimuli that may either be of interest or point to danger. Many aspects of attention are therefore involuntary and may often compete with task-focused attention, which is conscious (Bendixen et al., 2010). A burgeoning literature has examined the neurophysiological, cognitive and functional mechanisms for selective attention and attentional capture, which may divert attention from a target task (Banbury et al., 2001; Campbell, 2005; Hughes, 2014; Parmentier, 2008; Roer et al., 2017). In a recent book, Wickens and McCarley (2019) conceptualize attention on two levels. First, as one of three central parameters of information processing, together with storage for memory and the time it takes to respond. Second, attentional properties underlie many cognitive processes in that attention is required to retain information in working memory and to transfer material to long-term memory. Consequently, the concept of attention is complex and depending on a given task different attentional processes are utilized. For ease of analysis, attention is divided into sub-categories: focused attention which requires concentration on a particular task and the filtering out of non-relevant or competing stimuli; selective attention which allows for selection from a number of possible stimuli in order to focus on only the necessary stimuli required for a target task; switching attention from one task to another; divided attention, which

involves the parallel processing of two selected stimuli or tasks at the same time, and sustained attention which is used in continuous mental activity and reveals the capacity to focus on a specific task without being distracted (Posner, 1994; Prakash et al., 2008; Wicken, 2021; Wojtowicz et al., 2013). These sub-categories demand that attention be directed to stimuli for a target task and also involves the attentional ability to filter out unnecessary stimuli.

Attention is often referred to generically, however the present research focused on selective attention as it implies the selection of stimuli necessary to a task and the filtering out of irrelevant stimuli and information that are not useful. In the present research the SDMT and the Stroop test with embedded auditory distractors assessed the capacity of people with RRMS to selectively filter out the distractors in order to efficiently complete the test task.

Selective Attention

Selective attention is the mechanism whereby a person attends to particular stimuli or information and filters out distracting or irrelevant information. There is a limit to the amount of information that can be processed in a given period and so selective attention is vital in order to focus on necessary aspects of a target task. Selective attention involves two general concepts (Wickens, 2021). The first is as a filter that selects and allows in information from the environment to be processed and the second is as a resource to process the information according to task demands. Filtering requires supervisory control, noticing perceptual stimuli to be filtered by selective attention, so that a limited number of stimuli within an individual's capacity may be passed on for information processing. If attention is divided by distracting, irrelevant elements then attentional resources will be stretched, and may be constrained by a limit on cognitive resources. Thus, efficient cognitive depends on the ability to filter stimuli out that are not task-relevant (Parmentier, 2008).

Oberauer (2019) maintains that one definition of attention, essentially describing selective attention, portrays the process as a limited resource for information processing with mechanisms for the prioritization of information to be processed. Attention can be seen as attending to current sensory perceptions in the environment (mostly visual or auditory) and attention to information not currently perceived such as memories of events or concepts. Importantly attention that is controlled and consciously directed to pertinent goals, is referred to as 'top-down', while attention that is automatic, not goal directed, as 'bottom-up' (Oberauer, 2019). These aspects of attention will be detailed in the next chapter.

Attentional control and executive attention refer to the conscious capacity to choose what to attend to and what to ignore (Wickens & McCarley, 2019). Also, attentional control processes adjust the movement of information in and out of short-term and working memory. The method of selective attention, which is vital for the processing of target information, is influenced by three features. One, is prominence, when a stimulus is in contrast or highlighted with regard to surrounding stimuli. The second feature is novelty, which may create an attentional shift, and the third feature is the individual's attentional set or search for the stimulus. Salient stimuli which capture attention automatically, also referred to as bottom up processes are able to be consciously overridden by attentional top-down processes. Top-down processes entail executive attention which enables the performance of behaviours that are most important and supresses those that are not. This occurs when a given schema attains a dominant level of activation compared to competing schema as described in the Norman-Shallice Model (1986), the Supervisory Attentional System. The dominant schema thus inhibits the competing or incompatible schema.

Selective attention as a multifaceted construct entails the selection and filtering of relevant information as it has limited capacity in its role for information processing. It is hypothesized to

be an aspect of executive attention as the selective process involves 'top-down' control and retaining information for use in working memory (Wickens & Carly, 2019). The theoretical complexity in describing this form of attention will be evident in the next section.

Theories of Selective Attention

Since the focus in the present study is on auditory distraction and its impact on attention, relevant theories of attention and distracted attention will be discussed. Selective attention refers to the process of attending to certain stimuli, while ignoring others (Driver, 2001). Broadbent (1958), Treisman (1964, 1969) and Deutsch and Deutsch (1963), were pioneers in the development of selective attention theory and subsequent theory has built on the foundations they provided. The central question that concerned these theorists focused on the cause of difficulties in completing a cognitive task when the participant's attention was distracted and divided. Possibilities were that disruption either occurred when stimuli were first perceived (Broadbent, 1958), in an attenuated form (Treisman, 1964, 1969) or later (Deutsch and Deutsch, 1963). Early research on selective attention centred on the auditory modality.

Broadbent (1958)

One of the earliest and more influential of the early theorists on attention and distraction was Donald Broadbent (1958). He was concerned with selective attention and was the first to use an information processing model for theorizing about the attention processing system. Auditory information may come in many forms such as pitch, loudness, direction, semantic meaning, etc. Based on the characteristics of the words a selective filter allows certain stimuli to pass through for further processing and filter out others. Irrelevant information is abandoned before the content is processed. Broadbent (1958) used a dichotic listening paradigm for his research, whereby different information was fed through headphones to each ear at the same time, thus dividing attention. The research participant was required to focus on one message presented to one ear and

to repeat the contents, at the same time reporting on any changes of message presented in the other ear (Jones, 1999; Ross et al., 2012). In this task, participants filtered information using selective attention. Based on numerous of studies, Broadbent developed the Filter theory (1958), which postulates that there is a perceptual filter system that allows for some stimuli to pass through the filter for information processing and other stimuli to be lost. Broadbent's (1958) concept of attention likened information processing to a bottleneck that can only manage a single stimulus or item of information in a given period. The second stimulus must wait before the first is processed, thus reaction time is delayed. Due to the limited capacity of the information processing structure, by necessity there is an early selection of information. Broadbent was able to show that the difficulty in discriminating between information that is relevant and that which is not impaired performance resulting in diminished accuracy and speed in completion of the task. However, information that was selected to pass through the filter, could then be used by working memory. In essence, the process of a selective filter is necessary to protect a limited capacity system from overload due to an overwhelming amount of information that typically bombards the senses (Broadbent, 1958).

Treisman (1964, 1969)

There is considerable empirical support for Broadbent's (1958) theory, however, early sensory and perceptual processing is automatic and reflexive and not always subject to selective attention (Wickens & McCarley, 2019). Broadbent's (1958) theory was also criticized as it failed to account for the Cocktail Party Effect (Cherry, 1953). A party situation requires selective attention for concentrating on target speech while ignoring other speech that is not relevant to the target. However, attunement to events that occur peripherally is also neurologically hardwired, especially if those events have personal significance (Bronkhorst, 2015). Thus, the Cocktail Party Effect also allows for pertinent stimuli (for example one's name being called), to capture attention

(Har-Shai Yahav & Zion Golumbic, 2021). This effect was explained by Treisman (1964, 1969), who developed Broadbent's (1958) theory and proposed that unattended stimuli are not discarded, but are processed in an attenuated (weakened) form. To test this theory, Treisman (1964, 1969) increased the complexity of dichotic listening. In simple dichotic listening she found that a competing message in one ear did not reduce the ability of participants to follow and repeat a prose piece delivered through the other ear. Treisman then introduced two irrelevant messages on two separate channels broadcast from different locations at the same time as the participant was asked to listen to a prose passage. The results revealed that participants had a great deal of difficulty in reproducing the prose passage. This indicated that all the messages were processed at an early stage and the three competing channels caused overload in the system as attention was initially given to all channels. Also implied is that there was a compulsory attentional component rather than simply a discretionary attentional component. The greater the number of auditory messages the more the system is overloaded, that is, it has a limited capacity (Treisman 1964, 1969). Treisman then proposed that there must be a filter in selective attention that precedes analysis of the various streams of information. Based on this information, she developed a theory of attenuated attention, whereby unattended material is not disregarded, but is processed in a weaker form and may be retrieved at a later stage. The Attenuated Model adhered to the idea of bottleneck limited capacity processing, also stating that it is not possible to focus on all information presented without a filter.

Deutsch and Deutsch (1963)

The processing of unattended stimuli also occurs at a deeper cognitive level. Consequently, Deutsch and Deutsch (1963) proposed the Late Selection Model whereby all stimuli get processed at a later stage than that proposed by Treisman (1969), but are filtered before they become part of working memory. The late selection process operates according to

the semantic features of presented information. Since these early theories, the understanding of the neurophysiology of the brain has expanded and later theorists have come to understand that distracting stimuli are processed in different ways, both initially upon perception and at a deeper cognitive level, depending on the amounts of stimuli perceived and the difficulty of a task (Driver, 2001).

Perceptual Load Theory (Lavie, 1995)

This theory encompasses both early and late theories of selective attention. Late selection of stimuli for attention seems to occur in situations of low perceptual load when fewer stimuli are present, whereas when more perceptual stimuli are presented and attentional capacity is exceeded, early selection occurs (Lavie, 2005; Lavie 2010; Lavie et al., 2004). The theory makes three assumptions. The first is that attentional resources are limited in capacity, the second is that task-relevant items are processed before task-irrelevant items and third, all attentional resources are utilized. This theory is currently one of the preferred explanatory models for auditory attention and will be further explored in the next chapter (Murphy et al., 2017). In sum, perceptual processing is automatic, not under voluntary control, as long as there is available capacity. Therefore, all stimuli are processed, even those not required for the target task. Selective attention is vital for focus and the assimilation of necessary information to complete cognitive tasks and exclude extraneous stimuli. However, it may break down with excessive, unnecessary stimuli causing attentional capture (distraction) to these stimuli. This in turn may reflect a vulnerable cognitive 'filter' system. It is proposed that people with MS may be particularly vulnerable to this type of attentional capture (Adler & Lembach, 2015).

Petersen and Posner (2012) theorize that there are three networks that comprise the attentional system, based on neuropathology imaging of networks of active brain areas, when people perform simple cognitive tasks. The first is an alerting network which focuses on the

brainstem arousal system and is related to sustained vigilance during tasks. In this process a resting state is replaced by warning cues to expect a stimulus. The next is the orienting network which prioritizes sensory input by selecting a modality or location. The last network is the executive or focal attention system (top-down task control), similar to the description of selective attention which will be further explained in the next chapter (Petersen and Posner, 2012). The attentional system theory (Petersen and Posner, 2012) and the Perceptual Load theory (Lavie, 2005; Lavie 2010; Lavie & Hirst, 2004), provide an explanatory model for the present study's research question, namely 'Does auditory distraction impact processing speed in people with relapsing-remitting MS who test as cognitively intact on the MACFIMS compared to healthy controls?'. Since auditory distraction is central to the present research, theory and research involving the process of distraction will be explored in the following chapter.

The Role of Attention in Multiple Sclerosis

Significant deficits in focused attention and vigilance are commonly found in MS (Langdon, 2011). In MS neuropsychological assessment, attention is understood as the ability to inhibit competing and distracting stimuli (selective attention) and process target information in the form of executive attention (Jansen & Cimprich, 1994). In addition to processing speed, attention is a vitally important aspect of cognitive processing in MS and underlies many other spheres of cognitive functioning. There have been few studies in the field of MS aimed at purely attentional tasks, since the functions of processing speed and working memory (which require attentional processes) cannot be separated out (Chiaravalloti & DeLuca, 2008). Attention and speed of information processing domains are negatively impacted from initial stages in the disease and are significant reasons for impairment in memory or abstract reasoning (Calabrese, 2006). A few studies have explored attention in the MS population, however, the results highlight that attention cannot be parcelled out from working memory or

speed of information processing. An early seminal study of attention conducted by Kujala et al. (1995) reported that attentional difficulties in people with MS were related to reduced speed of information processing. Similarly, Paul et al. (1998) administered tests of selective and divided attention to MS patients and found that their results were significantly decreased compared to healthy controls on measures of complex attention, especially when working memory was impaired and responses were time sensitive. In a further study, Schultz et al. (2006) found that, in the early stages of MS, 10-38% of participants revealed significantly longer reaction time, deficits in attention and also reduced information processing speed. Deficits have been observed in focused, divided and sustained attention with real world implications, as people with MS who exhibited attention impairment were less likely to be employed than those who had intact attention (Schultz et al., 2006). Sustained and selective attention enables working memory to aid in speed of information processing necessary to current tasks and is a more common deficit together with difficulties in tasks of divided attention (Awh et al., 2006; Chiaravalloti & DeLuca, 2008). Similarly, Adler and Lembach, (2015) found significant variations between people with MS and controls in selective attention, working memory and short-term memory. Episodic short-term memory and selective attention in high demand tasks were significantly impacted. Additionally, impairment in attention, particularly due to divided or distracted attention, resulted in decreased processing speed. In a study of early RRMS, Amato et al. (2008, 2010) found impairments in complex attention (selective, alternating and divided attention).

MRI studies in relation to attention have examined patterns of brain activation, lesion distribution and network connectivity and revealed altered patterns of brain activation in people with mild RRMS on cognitive tasks of sustained attention, information processing speed and memory (Mainero et al., 2004). In addition, deficits in attention appeared to be

linked to a diffuse pattern of lesions with much slower response time on divided attention than sustained attention tasks (McCarthy et al., 2005). The connections of the structural networks involving attention and executive function are compromised in people with MS due to white matter and grey matter structural damage (Llufriu et al., 2017).

Conclusion

The functions of information processing speed, working memory and attention are vital to cognition and are interconnected to the extent that it is difficult to test these cognitive operations separately. Speed of information processing underlies the efficiency of these three linked processes (Chiaravalloti et al., 2013; Genova et al., 2013). Decrease in speed of information processing affects 40-70% of individuals with MS and arises when demyelination first occurs, even before a definite diagnosis of MS (Di Filippo et al., 2018; van Geest et al., 2018). Thus, by association problems occur in working memory and attention. Explanatory theories of information processing deficits propose that both simple and complex tasks are affected. Information processing speed is thus a necessary condition for efficient of information processing, more so than impairments in working memory, the latter which is also influenced by processing speed (Deluca et al., 2004; Chiaravalloti et al., 2013). However, underlying neuropathology can also lead to independent working memory deficits. Working memory is an adaptive system, which has limited capacity and is therefore reliant on speed of information processing before information is degraded or lost (Atkinson & Shiffrin, 1968; Baddeley & Hitch, 1974, 2019; Cowan, 1999, 2017). Importantly, selective attention, a vital component of working memory is necessary to discriminate target information, but is vulnerable to interference as many stimuli vie for attention. If there are more items for processing in working memory interference becomes stronger and attentional systems are required to inhibit interference. Therefore, attention becomes a ‘gatekeeper’ to separate items

that are necessary for the task at hand in the limited space in working memory. On the other hand, working memory maintains content to guide selective attention. Processing speed is impacted by the neuropathology of MS, which results in compromised selective attention when salient distractors are present. The theories and mechanisms of attention and distraction will be explored in the next chapter.

CHAPTER 4

SELECTIVE ATTENTION AND DISTRACTION

The senses are continually assailed by stimuli that require the exercise of selective attention in order to focus on relevant information. The most pervasive sensory stimulus is sound (Macken et al., 2009; Parmentier et al., 2019). We have the capacity to receive auditory signals from any direction, distance, and beyond the limits of our sight. We hear in the dark, even when we do not observe the source of a particular sound. Sounds alert individuals to stimuli of potential interest or danger and at some level the sensory system is always vigilant to the information that sounds provide. Thus, the processing of sound is neurologically obligatory, beyond conscious control, even when attention is directed elsewhere by distracting irrelevant sounds, which frequently break through selective attention (Banbury et al., 2001; Berti, 2013; Har-Shai Yahav & Zion Golumbic, 2021; Jones, 1999; Vachon et al., 2020). Auditory distractors are more potent than visual distractors (Leiva et al., 2015). Bendixen et al. (2010) studied the implications of cross-modal perceptual interference between auditory and visual stimuli. Irrelevant stimuli captured attention in both modalities, however task-irrelevant auditory distractions had a greater negative impact on task performance and endured for a longer period (Bendixen et al., 2010; Liebl et al., 2012). Since sound is ubiquitous it was chosen in the present study as the medium of distraction in target tasks that are visual in design. Cross-modal distraction that breaks through selective attention will be further explored in this chapter.

The focus of the present chapter is to understand how distraction disrupts selective attention and by extension the process whereby attention is regained in pursuit of a focal task.

This exploration sets the framework for investigating the research question in the present study, which is whether or not distracted attention results in speed of information processing impairment in people with RRMS. Auditory distractors were embedding in the SDMT and Stroop to assess the effects on processing speed in individuals with MS testing the hypotheses detailed in the next chapter.

This chapter presents a succinct summation of important theories of selective attention, which were explored in the last chapter, the theories and mechanisms of attentional distraction, and the ways in which attentional focus on a target task is lost and then regained. Additionally, the implications of auditory distraction on MS are discussed.

The following theories were explored in detail in the previous chapter; Broadbent (1958; Filter theory), Treisman (1964; 1969; Attenuation theory), Deutsch and Deutsch (1963; Late Selection model), Lavie (1995; Perceptual Load theory) and a summary will be provided as a link into the next sections. Broadbent (1958), developed an extensive explanatory model of selective attention and processes for filtering out irrelevant information. He asserted that there is an early perceptual filter that selects and permits necessary stimuli to be processed. Due to limited capacity stimuli cannot be processed in quantity, thus irrelevant stimuli are not processed and consequently lost. It is the discrimination between relevant and irrelevant information at an early stage that impairs performance in terms of precision and speed. Thus, the more the irrelevant information, the longer the time required to discern what is necessary or not to a target task. However, Broadbent's theory cannot adequately elucidate how unintended information gets through the filter. An example is the processing of sound, which is compulsory as individuals instinctively scan the environment for pertinent information. In order to explain this conundrum, Treisman (1964; 1969) maintained that unattended information is not completely filtered out or lost, but is retained in an attenuated form, a pre-

attentive stage, with the retention of elementary features or physical properties for example, shape and colour. Higher level processing occurs later and is dependent on attention which allows the perceptual qualities to be integrated as a whole concept including extracting attenuated information from memory. There is still limited capacity as attention is only able concentrate on one event at a time. Deutsch and Deutsch (1963) proposed that all stimuli get fully processed, but before entering into working memory the filtering of relevant information takes place. The criticism of this model is that the information processing system has limited capacity and not all stimuli can be processed in full, so some early filtration must occur. In order to explain the possibility that both early and late selection of perceptual stimuli co-occur, Lavie (1995; 2005; 2010; Lavie et al., 2004) developed the Perceptual Load theory. This unique conceptualization adds another dimension to the previous theories explored. It provides a framework for understanding the effect of more complex and cognitively taxing content on selective attention and the potential impact of distracting perceptual stimuli on working memory when greater cognitive challenges are required.

Distraction and Perceptual Load Theory

Essentially, Perceptual Load theory (Lavie, 1995) explains the relationship between perceptual load, which is the reception of perceptual information taken in via the senses, mainly visual and auditory, and cognitive load which is the volume of mental effort needed to complete a given task. The processing of information is dependent on the amount of information that is being received and the difficulty of the focal task.

In consideration of early and late selection of perceptual stimuli, the Perceptual Load theory proposes that when few perceptual stimuli are presented there is low perceptual load and spare attentional capacity enables a late selection of relevant material. An example of a task of this kind is naming the type of shapes in an image whereby a circle is surrounded by

rectangles. However, since perception has limited capacity when flooded with stimuli, that is with high perceptual load, only a certain amount of information can be processed and therefore early selection will take place. An example of higher perceptual load is naming the type of shapes with a circle surrounded by many shapes some of which are repeated. Early selection of information occurs when capacity is exceeded, resulting in some information being lost. Therefore, perceptual load is pivotal in determining the degree of efficiency of selective attention (Eayrs & Lavie, 2021; Lavie, 1995, 2014).

Irrelevant material that is processed is referred to as distractor processing. If the processing of relevant material does not take up all available perceptual capacity in situations of low load, then irrelevant material is involuntarily processed and conversely, if there is high perceptual load then irrelevant material to the task at hand is not processed (Konstantinou et al., 2014). Thus, distractor interference is found in circumstances of low perceptual load when all stimuli including task-irrelevant information are attended to. Conversely, under increased perceptual load distractor interference is far less (Eltiti et al., 2005).

Lavie et al. (2004), elaborated on two systems of selective attention and perceptual load. The first has already been explored and refers to a perceptual selection system that excludes irrelevant distractor stimuli in conditions of increased perceptual load. It is a more passive and automatic system, referred to as bottom-up selective attention. The second is a system of active attentional control which operates when there is high cognitive capacity demand. This form of attentional control is denoted as top-down selective attention (Oberauer, 2019). This mechanism rejects non-relevant distractors even though they are recognized in conditions of decreased perceptual load. Attentional regulation relies on higher cognitive mechanisms for example, working memory, and rejects irrelevant stimuli to remain goal-directed and ensure that stimuli that are not significant do not divert from the task at hand. Thus, cognitive controls

prioritize relevant over irrelevant information. These priorities are actively maintained in working memory so that available capacity is allocated to relevant information. If this does not take up all available capacity then remaining capacity involuntary processes irrelevant information at the same time (Konstantinou et al., 2014). However, Lavie (2005), found that when a task is more difficult there is higher working memory load and therefore, the possibility of more interference by a non-relevant distractor on the execution of a selected attentional task (Awh et al., 2006; Dittrich, 2012; Forster & Lavie, 2011; Lavie, 2010). Active and conscious focused attention is required to filter perceptual distraction and this competes with resources within working memory that are already involved in processing a target task. Thus, when tasks are more difficult and working memory is taxed, it is not effectively able to deal with both task and selectively controlling distractor interference. The result is reduced selective attention (Dittrich, 2012; Lavie, 2005, 2010; Lavie et al., 2004; Roper & Vecera, 2014). Thus, Perceptual Load theory (Lavie, 1995), takes into consideration the restricted ability of working memory, which as an adaptive system is only able to maintain and manipulate a circumscribed amount of relevant information that is accessible to current cognitive requirements (Adams, et al., 2018; Cowan, 2017; Spiller et al., 2012).

Perceptual load and working memory therefore, have opposing influences on selective attention. In other words, high perceptual load decreases distractor interference, but high cognitive load on tasks implicating higher cognitive processes, such as working memory, results in an increase in distractor interference. Confirmation of this first mechanism was provided by neuroimaging, which revealed that increased perceptual load in a goal-directed task attenuated neural activity connected to non-relevant distractors and even eliminated neural signals detected in fMRI related to potent distractors (Lavie, 2005). Neuroimaging research also indicates that visual cortex activity as a result of stimuli interference can be augmented by higher working

memory load. In this case, conscious cognitive control was required to focus on working memory tasks when distractor stimuli interfered. In sum, the capacity to focus attention increases in circumstances of high perceptual load, but deteriorates under these conditions when the individual is engaged in tasks that draw on higher cognitive functions (Lavie, 2010). The latter tasks require executive attentional control to remained focused on a task and to inhibit responses to irrelevant stimuli.[17] However, certain distractors are particularly potent or salient, such as surprise or novel stimuli, including auditory distractors, which capture attention. This results in working memory being taxed and breakthrough distraction occurring, which in turn delays response time. Frontal lobe functioning is required for such goal-directed behaviour, with working memory being heavily implicated, for example, the conscious filtering of distraction when selective attention is required for a cognitive task (Figueroa-Vargas et al., 2020). This becomes more difficult for people with MS as the frontal lobes are often impacted by disease burden (Benedict, Bakshi et al., 2002; Santiago et al, 2007). Consequently, people with MS were adversely affected by auditory distraction which was potentially related to some impairments in working memory (Lapoint et al., 2005; Lapoint et al., 2007). However, people with high working memory capability were able to selectively attend to a task and attenuated the effects of distraction (Sorqvist, 2010b; Sorqvist et al., 2012). The next section explores attentional distraction and the level of potency or saliency required to disrupt a target task.

Distraction and Saliency

The obligatory capture of attention by sound has been referred to previously. To adapt flexibly to new situations in the environment we need to identify unexpected sensory changes

[17] Chapter 3 outlined the mechanisms of attention, how incoming information is filtered and the role of the central executive in allocating relevant information for information processing in working memory (Baddeley & Hitch, 1974, the Multicomponent model; Norman & Shallice 1986), the Supervisory Attentional System; Cowan (1999), the Embedded-Processes model.

that surround us. This entails automatic processing of sensory input some of which is irrelevant and results in distraction from current activities to evaluate changes in the environment. This obligatory processing has cognitive consequences and can result in delayed response time and decreased accuracy in a given task (Berti, 2013). Separating task-relevant and task-irrelevant information (including diverse stimuli from the environment) is the function of the executive mechanism of working memory. However, some pervasive or salient auditory distraction that is unrelated to working memory capacity disrupts short-term memory and interruption from sound occurs even when the sound is ignored and is irrelevant to the task being performed (Campbell, 2005; Macken et al., 2009).

The central assumption in theories of distraction is that a change in sound has to be uncommon in order to significantly disrupt cognitive activity and draw attention away from a primary task (Roeber et al., 2009). Conversely, sound can contain changes and only be mildly disruptive. Studies of auditory distraction often compare three distraction sound sequences that differentially disrupt focus. These are first, steady state sequences (AAAAA), which are most susceptible to habituation. The second are deviation sequences, which entail one potent deviant sound in a steady state stream (AAABA) and third, changing-state sequences containing continuous changes from one distractor sound to another (ADBGXK), which result in recurring attentional shifts (Korner et al., 2019). It is unpredictable sound sequences, such as changing-state, that cause more interference than single deviation sequences (Roer et al., 2014).

Under certain acoustic conditions selective attention can break down and disrupt performance on a task. Auditory attention directs an acoustic evaluation of sounds of interest. As explored previously, attention can be top-down, voluntary, or bottom-up based on sound saliency or potency. Top-down attention creates a focus for cortical activity that is then directed to the most relevant sensory information to the task at hand, and executive attentional control is largely

able to consciously inhibit competing distractions to the relevant information. Bottom-up attention requires an automatic processing of information which needs to be filtered out (Fritz et al., 2007). Parmentier (2008, 2014) found that while study participants may learn to ignore standard repetitive sounds (AAAAA), the impact of novel deviant sounds (oddballs; AAABA) on task performance results in automatic attentional capture away from selective attention. An oddball test contains the continuous delivery of a sound stimulus (standard) and on sporadic, chance junctures the dispensing of different patterns of sound. Novel deviant sounds produce a stronger attentional diversion from a task (Parmentier & Andres, 2010). Roeber et al. (2009), asserted that deviant sounds result in longer reaction times and more errors on targeted tasks. These findings indicate support for Lavie's (1995) and Treisman's (1964) attentional theories, that is that irrelevant perceptual stimuli are automatically processed in varying degrees depending on perceptual and cognitive load.

There are two hypotheses that have been put forward as an explanation for the breakdown of selective attention and consequent interference with cognitive functioning. The one is disruption produced by varying auditory distractors, the changing-state effect (ADBGXK), and the other, by auditory stimulus that diverges from the background of sounds, the deviation effect (AAABA). The unitary mechanism posits that both processes capture attention[18], and the duplex mechanism suggests that they imply two particularly diverse types of distraction, and attentional capture is only caused by the deviation effect or novel sounds, and changing-state effects result in processing the sound followed by the orientating of attention to the sound (Marois et al., 2019). The latter causes information processing delays that are greater than the delays caused by the mere capturing of attention, which can be attenuated by working memory. Most studies contain

[18] Attentional capture refers to the unintentional focus of attention which causes a disengagement from a task (Korner et al., 2019).

serial recall tasks, which is a standard protocol for investigating the effects of background sound on cognitive performance. The tasks are presented in a visual or auditory mode, and then are rehearsed within working memory. Results remain mixed with regard to which of the two effects (unitary or duplex) is a better explanation for sensitivity to auditory distraction (Cowan, 1995, 1999; Marois et al., 2019; Hughes, 2014; Korner et al., 2019).

The Unitary Mechanism

This mechanism proposes that the diverse properties of sounds result in different mechanisms of distraction and consequently differential strength of disruption in attention. The deviation effect is the result of the unanticipated occurrence of an unusual sound that deviates from unitary background sounds, for example, AAAABA (Marois et al., 2019). A single deviant sound within steady-state sequences is a salient distractor resulting in attentional capture from a task (Korner et al., 2019). Alternatively, the breakdown in tasks requiring selective attention may be explained by the changing-state hypothesis. The changing-state hypothesis proposes that auditory stimulus of this type is obligatorily processed, resulting in a bottom-up automatic diversion of attention to the distracting sound (Lutfi-Proctor, 2016). Disruption in cognitive processing occurs when there is a changing-state sequence such as ABDF rather than a steady-state sequence, AAAA (Banbury et al., 2001). A changing sequence of sounds is far more disruptive than a steady sequence of sounds as sound is segmented into discrete entities each distinguishable from the previous sound (Jones et al., 2010). Thus, there are continuous changes from one distractor sound to the next resulting in repeated shifts in auditory attention, which forces automatic attention (Korner et al., 2019). It is theorized that changing-state distracting sound influences the processes of executive functioning that support active selection and manipulation of information resulting in impaired processing, which in turn may result in reduced processing speed (Banbury et al., 2001). Confirming this theory, Jones et al. (2010) found that

sound can significantly disrupt a visually presented task and that short-term memory may show up to 25% retention loss with auditory distraction. Change in a sound sequence rather than a steady state sound appears to be one of the key determinants of distraction. Speech is a particularly good example of a changing-state sequence and irrelevant speech is particularly powerful in breaking down selective, task-focused attention (Banbury et al., 2001; Beaman & Holt, 2007; Bell et al., 2011). The current study utilized this paradigm to investigate the saliency of embedded irrelevant speech as a distractor to explore the impact on speed of information processing. The potency of speech distraction will be explored later in the chapter. The Embedded-Processes model of Cowan (1995, 1999) is the theoretical foundation for the unitary explanation. It suggests that the changing-state and the deviation influences result in auditory capture. When deviant or changing novel sound occurs that is irrelevant to the present auditory event there is an automatic orienting of attention to this stimulus. Thus, both types of distracting sounds produce similar, automatic, bottom-up attentional disruption. (Marois et al., 2019).

The Duplex Mechanism

Attention is captured by sounds that are different, that is, not expected or predicted by previous sound streams. According to the duplex mechanism the deviation and changing-state effects capture attention in different ways. There is habituation to deviation effects in that working memory can predict deviation, which allows for top-down attentional control. However, changing-state effects automatically result in an orientation toward the sound. Thus, attention is always disrupted (bottom-up) by a changing-state sound and auditory distraction created by changing-state sequences is somewhat resistant to top-down attentional control in contrast to single deviant sounds (Hughes, 2014; Sorquist, 2010a). Top-down attention, also referred to as voluntary attention, allows an individual to perform tasks in a goal-directed way. In this scenario selective attention is able to filter out irrelevant sensory stimuli such as deviant sounds from a

target task (Parmentier, 2008). The individual is able to consciously and selectively focus on a target task and exclude distractions. In contrast bottom-up attention is reflexive (involuntary), forcing attention to be orientated or diverted automatically to new stimuli and the latter occurs in the presence of changing-state sequences.

Working memory co-ordinates distracting stimuli in terms of what is important for environmental alertness and what is in the service of a current task (Berti & Shroger, 2003). Korner et al. (2019) found that the extent of distraction in terms of both deviant sounds and changing-state sounds was determined by the cognitive load placed on working memory. When tasks are complex or involve memory load there are not sufficient attentional resources to utilize top-down attenuation of the distractor sounds (Dalton & Hughes, 2014; Lavie, 2005; Parmentier, 2014). Thus, when cognitive load is increased it is more difficult for attentional control in working memory to sift through relevant and irrelevant information. When working memory is most taxed (high cognitive load) deviation and changing-state distractors negatively influenced cognitive performance and when the burden on working memory is low the attentional capture is lower (Sorquist, 2010a). This reiterates the Perceptual Load theory of Lavie (1995). Thus, there is an increase in the effect of distraction when working memory or cognitive load is high and it becomes difficult to process and differentiate multiple streams of information, to inhibit some and attend to others, in order to complete a cognitive task (Zeamer & Fox Tree, 2013). Since the ability to filter out irrelevant stimuli is highly mediated by working memory capability, individuals exhibiting high working memory ability are more equipped to inhibit irrelevant information from entering into working memory (Sorqvist et al., 2012) They are able to sustain attention on a focal task when subject to irrelevant sound and thus exhibit decreased vulnerability to the deviation effect (Hughes, 2014; SanMiguel et al., 2010). However, high working memory

capability can only mitigate the deviation affect and not the changing-state effect (Sorquist et al., 2012). This is because changing-state sounds result in an automatic diversion of attention.

The impact of sensory distraction on neurological functioning has been studied in order to obtain neurological correlates of impaired cognitive performance. The research that is discussed in the following section substantiates the Duplex mechanism in that changing-state sounds create an automatic diversion of attention (Hughes et al., 2013; Smucny et al., 2013).

Neurological Responses to Distraction

The ability to limit distraction is vital for goal directed activities and efficient filtering is essential for optimal performance (Zanto & Gazzaley, 2009). These processes are reflected in neural activity. Neural networks involved in task focus and auditory distraction are mediated in the dorso-lateral prefrontal cortex and activity in this area maintains task relevant information in working memory. When interfering information triggers conflicting brain activation, that is between the task on one hand and attentional capture by the distractor one the other hand, the dorso-lateral prefrontal cortex increases attentional resources towards working memory and therefore, the task at hand (Weissman et al., 2004). Thus, working memory functioning is reliant on efficiently filtering out non-relevant information utilizing neural suppression to avert over taxing the limited memory ability, and top-down goal targeted control is related to enhanced neural activity to pertinent material and suppressed neural response to non-relevant stimuli (Dalton et al., 2009; Kollndorfer et al., 2014). Under conditions of high cognitive load increased neural resources are required when distractor noise is present (Campbell, 2005). There is decreased response to noise under conditions of low difficulty and increased neural response to noise in conditions of high difficulty, as greater response inhibition is required. It is unpredictability in noise stimulus, such as that produced by changing-state sounds that most taxes the processes of response inhibition (Smucny et al., 2013). In order to explore the process of

attentional capture by distractors, numerous studies have been undertaken to measure brain responses to sensory events using ERP tests, which are measured by means of an electroencephalogram (EEG). These studies lend support to the top-down, bottom-up attention principle (Berti & Schroger, 2003; Berti, 2013; Dalton & Hughes, 2014; Marois et al., 2019; Parmentier, 2008; Parmentier et al., 2008; Parmentier & Andres, 2010; Ponjavic-Conte et al., 2012).

On the basis of these studies, a three-stage model has been proposed in the neurocognitive system that underlies distraction, or disruption to the attentional network (Berti et al., 2013). The first stage is a pre-attentive change detection, which automatically processes incoming sensory information and can detect novel or deviant aspects. Second, an involuntary orientation of attention is triggered to evaluate new sensory information, and third, reorientation to the task at hand follows only using information if it is relevant to the target task (Berti, 2013; Getzmann et al., 2022). The first two stages are involuntary, automatic bottom-up responses, and the last is a voluntary, top-down response (Petersen & Posner, 2012). As measured with ERP tests, in the first stage, the task-irrelevant distraction elicits a mismatch negativity (MMN), which occurs in auditory perception when sound changes or deviates rather than remains repetitive. The result of the mismatch negativity (stage two) is an involuntary turning of attention to new information, a novel sound, causing attentional disruption (called the P3a or novelty P3). The P3 is employed as an indicator of attentional processing (Wickens & McCarley, 2019). The final stage is a re-orientating to the task at hand, known as the re-orientating negativity (RON; Ponjavic-Conte et al., 2012).

The present study is cross-modal in that auditory distraction, in the form of unintelligible speech, was inserted into visually-based tasks. Neurological reactions to auditory and visual distraction differ in response time. Rare auditory stimulants distract visual information processing

and information as observed on ERP tests, which is mirrored in delayed reaction time, but not necessarily in error rate (Berti, 2013). Five experiments revealed that response latencies in visual tasks were longer following the presentation of novels sounds compared to standard sounds. These novel sounds underwent further processing which was underpinned by frontal networks in the brain (Parmentier, 2008). For example, a continuous stream of speech creates a deviant sound stream compared to generalized broadband noise and results in a time delay between auditory events and brain responses. This is because speech processing modifies neural activity connected with auditory working memory and attention, which is evident on cortical ERP readings (Ponjavic-Conte et al., 2012).

Information obtained from ERP tests is compatible with Baddeley's (1992) position that auditory spoken information is automatically processed by the phonological loop and, therefore, working memory is disrupted by speech-like auditory distractors. Although, there is little immediate top-down control of the distracting consequences of speech disruptions, these effects may be ameliorated in individuals who have high working memory capability (Sorquist, 2010). Despite automatic attention to the changing-state of speech, reorientation is much quicker in these individuals. People with high working memory ability may recover more quickly from the influences of changing-state distraction in the form of speech than those with low working memory capacity (Sorquist et al., 2013). This idea also echoes in Lavie's theory (1995, 2005, 2010) of selective attention in that higher cognitive processes require conscious effort to selectively attend to a task and ignore distractors. However, with weaker working memory as seen in many individuals with MS, the attenuating features of high working memory capacity, known to deal more efficiently with distraction, are diminished (Diamond et al., 1996; Randolph et al., 2017). The current research is centred on the hypothesis that a high percentage of people with MS are impacted in this way by distracting sound in focal tasks. This distraction is

particularly powerful in the context of speech patterns, which are changing-state, and thus more disruptive to working memory and consequently selective attention (Marsh & Jones, 2010; Marsh et al., 2018).

Speech as a Salient Distractor

There is a hierarchy of difficulties linked to distraction in that some distractors are stronger than others in disrupting cognitive activities. Reaction times are increased when using both verbal and non-verbal auditory distractors, however, speech is particularly powerful in breaking down selective attention due to the changing-state effect (Banbury et al., 2001; Beaman & Holt, 2007; Dittrich & Stahl, 2012). Working memory, which is tasked with inhibiting interference from distractors, is attuned to processing speech-like information whether or not it is relevant to an ongoing task (Bell et al., 2011). The capture of attention by spoken sounds, whether intelligible or unintelligible is followed by automatic semantic processing and this can be potent enough to linger for a period in working memory and interfere with a target task (Bell et al., 2011). Speech inherently contains more acoustic variety than non-speech items. The irrelevant speech effect results in greater amplitude on the mismatched negativity revealed in the frontal regions of the brain by ERP readings compared to the non-speech effect. These ERP tests highlight the diversion of attention to the new stimulus of information (Zanto & Gazzaley, 2009). Thus, speech produces pronounced irrelevant sound effects and greater attentional resources are needed to deal with changing-state speech than non-changing state sounds (Little et al., 2010). Even sounds with speech-like properties produce more disruption than sounds that do not have this quality and these acoustic fluctuations decrease task performance (Kattner & Ellermeier, 2018). Additionally, speech has obligatory access to memory (Banbury et al., 2001). For example, performance on serial recall is significantly affected by background noise, in particular speech (Beaman, 2005).

Interference from to-be-ignored speech also increases with multiple changes in pitch and amplitude. In the workplace, speech is the most distracting sound and can decrease productivity by at least seven percent (Hongisto, 2005). In a simulated office environment irrelevant speech significantly reduced task performance and two simultaneous talkers were more distracting than one voice (Yadav & Cabriera, 2019). For these reasons, the present study used unintelligible speech as a particularly potent distractor for people with MS, since a high proportion of these individuals are already compromised with respect to attention and processing speed.

A few studies contain embedded speech as a distractor using various formats that are acoustically presented such as, speech played backwards, lists of spoken words, foreign languages, multi-speaker babble and four-speaker babble (Beaman & Holt, 2007; Bell, et al, 2011; Halin et al., 2014; Hughes, 2014; Jones & Macken, 1995; LaPointe et al., 2007; Liebl et al., 2016; Marsh et al., 2009). Although semantic evaluation of incoming information occurs, it appears that actual semantics (the meaning of speech) plays little role in the inherent distracting qualities of speech (Crinion et al., 2003). It is the acoustic quality of irrelevant sound that regulates the degree of non-relevant sound effects and speech is especially distracting as it comprises numerous unexpected changes from one expression to the following one (Beaman & Holt, 2007). Ongoing vigilance for speech-like sound is neurologically primed and narrative speech, even if meaningless, does not disrupt a target task more than reversed speech, which is largely incomprehensible, or speech in a language that an individual does not know (Marsh & Jones, 2010). Even the intensity or loudness of sound is not necessarily a significant factor in determining degree of distraction (Beaman, 2005). However, the effect of backward speech compared to comprehensible forward speech results in a significant reduction in performance. It is the search for meaning in unusual sounds that results in the greatest

distractor interference as working memory is required for this task, potentially interfering with a target task (Nager et al., 2001). The impact of distractor multi-talker babble on cognitive tasks compared to non-distractor trials resulted in greater cognitive effort as measured on ERP tests and in decreased performance accuracy (Roer et al., 2014). However, it seems that the number of voices presented has a bearing on distractibility. Disruptive effects of speech increased from one to two to three voices, but decreased above three voices as the various sound tracks start to mask one another and the sound waveform is flattened (Banbury et al., 2012). So, a continuous babble of voices is less distracting than a restricted number of voices. When sound waveforms contained variations, a 'changing-state' component of irrelevant noise was reproduced. Speech with its abrupt changes in frequency and pitch is a particularly good example and created a varied waveform (Beaman & Holt, 2007).

When irrelevant speech effects are present the impact on cognition is continuous and does not dissipate rapidly (Beaman & Holt, 2007). Using the Multimodal model (Baddeley & Hitch, 1974) as a framework, irrelevant speech uses capacity in the phonological loop and people with low working memory capacity, such as individuals with MS, are particularly affected. Conversely, individuals with higher working memory capacity made fewer errors when subjected to auditory distractions in the form of irrelevant speech intrusions (Beaman, 2004). In support of Perceptual Load theory (Lavie 1995), when research participants were subjected to background speech noises, recall was better with more difficult-to-read than easy-to-read passages when speech background noise was playing. Increased task difficulty facilitated increased selective attention (Halin et al., 2014; Sorqvist, 2012).

In sum, speech impairs performance more than other sound conditions and variable speech-like sounds cause greater impairment than continuous speech-like noises. Speech results in a changing-state sequence of sound. Decreased performance on a target task occurs

due to the automatic processing of the distracting sound, since both distractor processing and cognitive tasks compete for the same cognitive resources (Liebl et al., 2016; Oberauer et al., 2016; Romei et al., 2011).

Cross-Modal Distraction

Most sensory stimuli arise from auditory and visual modalities. Visual and auditory information is processed in the brain at different speeds. Visual information reaches higher processing later than auditory information, which results in task irrelevant visual changes (distraction) being less disruptive than task irrelevant auditory changes (Bendixen et al., 2010).

The present study examined the impact of auditory distraction on visual functioning tasks in a cross-modal paradigm. Cross-modal studies of distraction have been conducted particularly with regard to auditory and visual modalities (La Pointe et al., 2005; Lewald & Guski, 2003; Parmentier et al., 2008). Performance on a visual discrimination task was affected by auditory deviant or novel sounds (Parmentier et al., 2008). This was particularly evident in more difficult processing tasks which then elicited a stronger orienting response (RON). Using a cross-modal design, the effects of auditory and visual distractors were assessed and interference between modalities occurred. Task-irrelevant changes were always detected even when attending to the other modality and both types of task-irrelevant stimuli interfered with the processing of task-relevant information in the other modality (Bendixen et al., 2010). However, cross-modal interference by auditory stimuli was more pronounced on visual tasks than vice versa. Also, the effect of auditory distraction on visual task-related processing extended over a longer time-span. By contrast, visual distraction occurred in a very narrow time period, therefore attentional recovery was much quicker (Bendixen et al., 2010). The reason that the impact on task performance by auditory stimuli is greater than visual stimuli is that visual information reaches higher cognitive processing at a slower rate than auditory

information by about 50-100ms (Bendixon et al., 2010; Lewald & Guski, 2003). Thus, visual changes are less likely to trigger the orienting-reorienting response typical of auditory stimuli. Consequently, the latter have a higher environmental alerting potential. In another cross-modal study, it was observed that distraction was evident for auditory distractors irrespective of the modality of the task, whereas visual distractors did not result in notable deviation from the visual or auditory task, strengthening the contention that auditory distractors are particularly potent (Leiva et al., 2015). For these reasons, auditory, rather than visual distractors were selected for use in the present study. Distractors in the form of four-person babble with word repetition, significantly impaired reactions times on visual processing tasks in MS participants in comparison with control participants (LaPointe et al., 2005). These findings informed the rationale in the present study to explore cross-modal distraction and embed auditory distractors in the SDMT and the Stroop, which are visually-based tests.

The visually presented tasks in the present study, the SDMT and Stroop, are robust predictors of impairment in processing speed in MS (Benedict et al., 2008; Benedict et al., 2012; Brochet et al., 2008; Deloire et al., 2006; Denney & Lynch, 2009; Drake et al., 2010; Langdon et al. 2012; Hughes et al., 2013; MacNiven et al., 2008; Parmenter et al., 2007; Sonder et al., 2013; van Schependom et al., 2014). Few studies of cross-modal auditory distraction in the Stroop have been undertaken. Using a variety of auditory speech distractor conditions, results on the Stroop revealed that, although there were longer reaction times between distractor and non-distractor trials, these were not significantly different (Elliott & Cowan, 2001). Non-relevant distractors that were not associated with the target task, largely did not cause interference. Participants could disregard irrelevant visual information that did not contain words in a cross-modal Stroop, but could not filter out irrelevant auditory information

(Lutfi-proctor et al., 2014). The next section discusses the few available studies, which explored the relationship between performance on the SDMT and distractors.

Multiple Sclerosis, Attention and Distraction

A primary hypothesis in the present study was that people with RRMS who tested as cognitively intact on the MACFIMS took longer to perform the SDMT and the Stroop with auditory distractors compared to the healthy control group. In the following section there is a discussion relating this difficulty to greater involuntary distraction in people with MS and difficulties in reorienting attention to the target task.

From the early stages of MS working memory capacity is impaired and is associated with more impaired executive functioning (Berrigan et al., 2013). Generally, people with MS have difficulty maintaining focus on a task which is likely the result of attentional dysfunction (Clough et al., 2018). Limited research has focused on attentional distractors and cognition in MS, and further research is vital to create a theoretical framework to understand the impact of auditory distraction on cognitive processing in people with MS. The studies that have been undertaken reveal that MS participants were susceptible to task disruption if a verbal distractor was complex and long in duration. Participants were more distracted when the time of the distractor increased from 5 to 15 seconds, which impaired performance in speed and accuracy when compared to matched controls on tasks of sustained and divided attention (Diamond et al., 1996; Diamond et al., 1997; McCarthy et al., 2005). LaPointe et al. (2005) explored the impact of speech on visually presented cognitive tasks to assess reaction time and visual memory in people with RRMS. The tasks assessed visual processing and visual cognitive functioning. Differences were measured on reaction times and accuracy scores. Participants were presented with three different irrelevant speech distractors using a counter-balance methodology. First, four-talker babble was presented simultaneously with two men and two women reading from different passages. Second,

interjected words played continuously, which participants had to repeat while engaged in the target task, and third, four-talker babble was presented with interjected words. These cognitive tests were all reaction time tests and results revealed that auditory distraction, particularly linguistically discernable words (compared to tones or nonsense syllables), resulted in significantly slower reaction times in individuals with MS in comparison to healthy controls. The more complex the task, the greater the decrease in performance, as auditory competition and distraction added to cognitive resource allocation (LaPointe et al., 2005; La Pointe, et al., 2007).

In a study that has direct bearing on the choice of speech distractor used in the current study, speech impaired performance significantly more than other acoustic distractors and variable speech-like noise impaired more than continuous speech-like noise (Liebl et al., 2016). Twenty-three people with MS completed a cognitive battery during counterbalanced auditory conditions, utilizing quite/standard conditions and distraction conditions with random office noise. The two groups were comprised of those who believed they were cognitively impaired and those who believed they were cognitively intact. People with MS with more self-disclosed cognitive complaints were vulnerable to environmental distraction, which particularly impacted processing speed, compared to the MS group who believed themselves to be cognitively intact. Thus, auditory distractors in the form of random office noises affected processing speed in participants who reported cognitive impairment and were aware of their dysfunction. Results on psychometric tests did not show significant variance between the MS groups on the DK Color-Word Interference test, the PASAT 3 the second trial CLT-11, the total learning and the DK Trails Number Letter. The only difference between the groups was found on the SDMT (Randolph et al., 2017).

This type of experimental design utilizing ecological validity is more predictive of real-world functioning. In order to improve the validity and sensitivity of the computerized version

of the SDMT (c-SDMT), other studies have incorporated ambient office sounds, for example, distractors in the form of telephone rings and car horns were embedded in the c-SDMT and compared with a non-distractor version of the traditional SDMT (Patel et al., 2017). Ninety-nine people with MS (including all disease subtypes) were compared to 55 healthy controls. The groups were divided with the first half doing the non-distractor SDMT and MACFIMS and the second half the distractor SDMT with the MACFIMS. The c-SDMT was undertaken before the MACFIMS to reduce practice effects from doing the SDMT twice as it was also part of the MACFIMS. The mean time of the c-SDMT was significantly greater in MS participants compared to the healthy controls. Additionally, significantly more MS participants had deficits on the c-SDMT with distractors than the conventional SDMT. However, no difference was noted on the c-SDMT with and without distractors. The sensitivity and specificity on the c-SDMT with distractors in revealing cognitive impairment was 81% and 88% percent respectively, on the c-SDMT without distractors, 60% and 79% and the conventional SDMT 61% and 96%. This result showed the added strength of including distractors to reveal cognitive impairment. As an additional aspect of the research, the MS group was separated into those with higher cognitive reserve and those with lower cognitive reserve. The SDMT with distractors was capable of revealing significant cognitive impairment in the high reserve cohort in contrast to the traditional SDMT. Difficulties in adequately screening out distractors unmasks attentional deficits, which can also be observed in attentional blindness.

Inattentional blindness is portrayed as ‘looked but failed to see’ effect, a perceptual blindness, when failure of attention leads a participant to overlooking an obvious item in visual sight. (Wickens and McCarley 2019). It occurs when the environment contains many sensory stimuli overloading the system and selective and focused attention are impaired. Attention requires the inhibition of distractions and so less inattentional blindness is associated with

heightened distractibility. People with MS were tested on the MACFIMS, the Stroop, and Gorilla in the Room test. This last test assesses inattentional blindness. Participants viewed a 30 second video clip in which they had to count passing basketball throws by a team wearing a white uniform while a person dressed in a gorilla suit walks across the room. Although no differences in counting ball-throws or noticing the gorilla were found in healthy controls and people with MS or between cognitively intact and impaired individuals with MS, the participants who revealed deficits on the Stroop and PASAT 2 (Paced Auditory Serial Addition Test – 2 seconds) were more likely to detect the gorilla and counted fewer ball passes (Feinstein et al., 2012). This may explain why some individuals with MS who test as cognitively intact on neuropsychological batteries such as the MACFIMS still struggle with real-world challenges in multitasking and inhibiting distracting stimuli.

In conclusion, ecological validity in MS research entails that researchers should consider sensitive methods of understanding the real-world effects of distraction on cognition in people with MS. Distraction resulting from speech is pervasive, affecting many situations requiring selective attention, including work and education settings. The present research refined the Patel et al. (2017) study by including speech distractors which were changing-state and hypothesized to be more distracting than the deviant sounds such as telephone rings and car horns (Beaman & Holt, 2007). The speech distractor that was used in the present research contained two voices, male and female, conversing, but with the speech intelligibility content largely masked. This allowed for variability in pitch and sound, reproducing a changing-state pattern of English-language cadence. The choice of this type of auditory distraction was aimed at revealing impairment in information processing speed in people with RRMS using a more ecologically valid paradigm.

The next chapter focuses on the methodology and design used in this research, including aims, rationale, hypotheses, participant inclusion, procedure, tests used, ethical considerations and description of data analysis.

CHAPTER 5

METHODS

Introduction and Aim of the Research

Up to 40% of people with RRMS are known to experience cognitive impairments, with processing speed a cognitive domain particularly impacted from the earliest stages of MS (De Sonneville et al. 2002; Glanz et al., 2012; Olivares et al., 2005). The primary goal of the current research was to evaluate the effect of distracted auditory attention on processing speed in people with RRMS who were found to be cognitively intact on the most extensively utilized and consensus derived neuropsychological battery for MS, the Minimal Assessment of Cognitive Functioning in Multiple Sclerosis (MACFIMS). The initial group of RRMS participants was divided into two groups according to scores obtained on the MACFIMS. Those who passed according to the assessment criteria were named the cognitively intact group, and those who failed constituted the cognitively impaired group.

The aim of the research was to test whether the inclusion of the speech-like auditory distractors embedded in the Stroop and the SDMT were more sensitive than these tests without such distractors, in revealing cognitive impairment in the cognitively intact group. This group was the focus of comparison with the control group as it was hypothesized that subtle cognitive impairment is not revealed in traditionally implemented assessments. As such it was proposed that the two tests with distractors would reveal deficits that did not manifest on the MACFIMS battery.

Research Design

The research design was a 4×2 between group comparison. It was quasi-experimental in nature, as assignment to the cognitively intact and cognitively impaired MS groups was not random. The RRMS group was divided according to functioning on the MACFIMS into the cognitively impaired and cognitively intact groups. The scores obtained by these groups on the MACFIMS were used for comparison. In order to have as much equivalency between the groups as possible, the entire RRMS group of 79 was matched to the healthy control group in terms of inclusion and exclusion criteria, age, gender, years of education and counterbalance design. Statistical analyses for the three groups, intact RRMS, impaired RRMS and healthy controls included within and between group comparisons. For within group analyses there was a repeated measure design in that each group was compared to itself on the same measures, the Stroop and the SDMT, under two conditions (with and without distractors). Between group comparisons with the three groups evaluated differences on both the Stroop and the SDMT, with and without distractors.

Variables

The independent variables were group (MS or control), age, gender, years of education, WTAR, degree of disability (EDSS), duration of disease, depression scores, employment status and counterbalance groups. The two counterbalance groups were constituted according to whether the SDMT and the Stroop were undertaken with distractors first or without distractors first. The dependent predictor variables were the SDMT and the Stroop each utilizing two versions, without distractors and with embedded auditory distractors in the form of unintelligible speech. Figure 5.1 below depicts the research design including the three groups, between and within group comparisons.

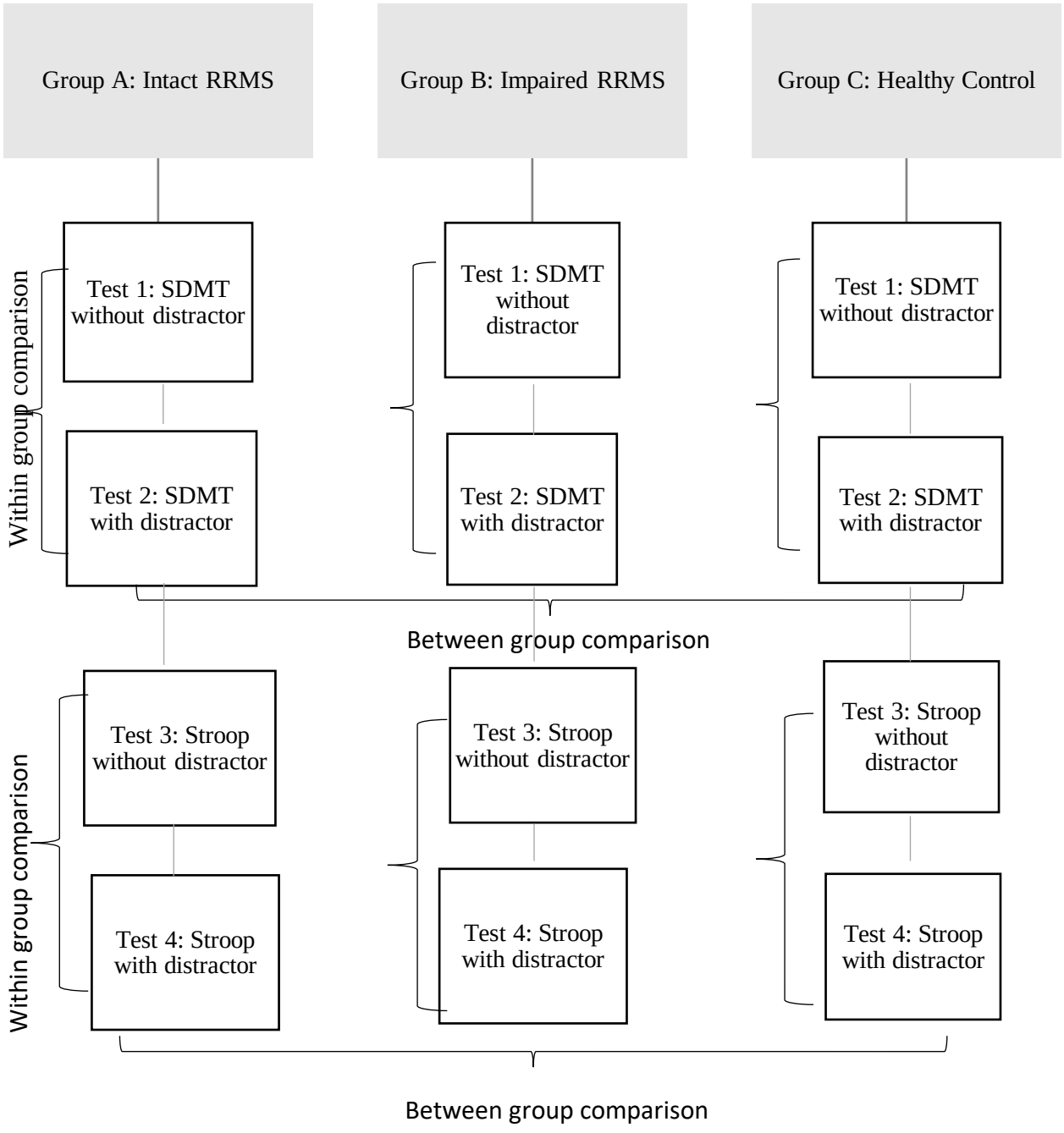


Figure 5.1

Research Design

Primary Research Question

The primary research question addressed the central aim of the research, namely, *Does auditory distraction impact information processing speed in people with RRMS who test as cognitively intact on the MACFIMS compared to healthy controls?*

Hypotheses

The between-group hypotheses compared two groups, namely, healthy controls and those who were cognitively intact within the RRMS group, on the SDMT and the Stroop with and without distractors. It was hypothesized that the addition of distractors to the SDMT and the Stroop would reveal further evidence of cognitive impairment, particularly cognitive impairment in the form of decreased information processing speed. This hypothesis explored whether distractors were able to reveal cognitive deficits in the cognitively intact group that were not apparent on the MACFIMS, the traditional cognitive MS assessment battery. Although errors scores are rare these were also compared.

The following hypotheses were tested:

Between Group Comparisons

1. The cognitively intact RRMS group would take longer to complete the SDMT with distractors than the healthy control group on the SDMT with distractors.
2. The cognitively intact RRMS group would have a greater number of errors on the SDMT with distractors than the healthy control group on the SDMT with distractors.
3. The cognitively intact RRMS group would take longer to complete the Stroop with distractors than the healthy control group on the Stroop with distractors.
4. The cognitively intact RRMS group would have a greater number of errors on the Stroop with distractors than the healthy control group on the Stroop with distractors.

Within Group Comparisons

In addition to the between group analyses, it was further hypothesized that distractors embedded in the two tests would result in longer processing speed than the two tests without distractors. This would entail comparisons within each MS participant group. The importance of these hypotheses was that the SDMT and the Stroop with distractors would have greater sensitively in detecting cognitive impairment across both relapsing remitting groups than the same tests without distractors. The following hypotheses were tested:

5. The cognitively intact RRMS group would take longer to complete the SDMT with distractors than the SDMT without distractors.
6. The cognitively intact RRMS group would take longer to complete the Stroop with distractors than the Stroop without distractors.
7. The cognitively impaired RRMS group would take longer to complete the SDMT with distractors than the SDMT without distractors.
8. The cognitively impaired RRMS group would take longer to complete the Stroop with distractors than the Stroop without distractors.

Sample

All participants were Canadian and English was their first language. Racial demographics are not taken in Canada, however, in this sample over 95% of the participants were white. Worldwide the majority of people diagnosed with MS are white, therefore, participants' demographics in this study were consistent with global demographics (Mascialino et al., 2019). All participants volunteered and were required to meet inclusion and exclusion criteria. The inclusion criteria necessitated that people who participated in the research had a confirmed diagnosis of RRMS given by a neurologist using the McDonald criteria and were between the ages of 18-60 years (Polman et al., 2005, 2011). This age range

was chosen because it followed the research protocols in an extensive MS neuropsychological literature (Akbar et al., 2011; Rosti et al., 2007; Schultz et al., 2006; Smith et al., 2012; Summers et al., 2008; Sumowski et al., 2009). The age range for the development and diagnosis of RRMS is 20-40 years, although there are some new diagnoses up to the age of 50 years. The disease course, rather than age is indicative of cognitive impairment (Amato, Zipoli & Potaccio, 2006, 2008; Deloire et al., 2006; Huijbregts et al., 2004; Moccia et al., 2016). Eighty-five percent of RRMS individuals will go on to develop SPMS after approximately 15 years. In at least 15% of individuals, the disease does not become progressive. Therefore, it is standard to recruit people with RRMS to cover the range of 18-60 years. It also allows for the research findings to be compatible with the broader MS literature and for the tests to be more widely applicable to the RRMS population (Akbar et al., 2011; Benedict, Cookfair et al., 2006; Benedict et al., 2008; Feinstein et al., 2013; Hughes et al., 2013; Moccia et al., 2016).

Participants were not included if they exhibited visual acuity of below 20/70 corrected,[19] were colour blind, had severe physical or psychiatric diagnosis (this included substance abuse), previously had a traumatic brain injury, learning disability, diagnosis of another neurological disorder, or had undergone neuropsychological assessment in the previous year. This information was collected from the demographic questionnaire (Appendix C). Participants were also asked in the demographic questionnaire if they experienced a hearing deficit. This information was cross-checked with the treating neurologist. The reason that this question was asked was that auditory distraction was central to the research question and therefore it was vital that hearing was intact for inclusion in the study. It is interesting to note that although hearing loss occurs in people with MS, it is generally associated with symptom exacerbation or an attack, and in the majority of cases individuals recover and return to baseline

[19] This number follows the protocol of the MACFIMS validation study (Benedict et al., 2006).

(Hellmann et al., 2011). A study comparing hearing acuity in pure tone thresholds between 5 and 10 dB found that there was a difference between controls and people with MS. When the MS group was divided into relapsing remitting and secondary progressive, the latter group performed more poorly than the former. The researchers reported no difference between the three groups on word recognition scores when words were presented in the auditory modality (Lewis et al., 2010). These authors also reported a return to baseline for the majority of people with MS who experienced hearing loss.

In the current study, there were two parts to the sampling, namely the RRMS participants and healthy controls. For the former group, 80 RRMS participants were tested, as there had to be a minimum of 30 people in each group to conform to the requirements of the Central Limit Theorum so that normality of data distributions could assumed (Salkind, 2012). As referred to previously, it was anticipated that the cognitively intact MS group would comprise approximately 60-70% and the cognitively impaired MS group 30-40% of the sample. Based on these percentages up to 80 MS participants would need to be tested. Therefore, the reasoning was that the number of cognitively intact people with MS (N = 45-50) would be greater than those who were cognitively impaired (N = 30-35). Due to missing data, one participant of the RRMS group was excluded and therefore only results of 79 participants were included. Based on the results of the MACFIMS the relapsing remitting group contained 46 cognitively intact and 33 cognitively impaired participants. For comparative purposes a healthy control group, comprised of 50 people, was recruited and underwent the identical assessment protocol to that of the participants with MS. They were matched to the MS group by age, gender, level of education, and IQ assessed on Wechsler Test of Adult Reading (WTAR) scores (see rationale for use of this test in the Instruments section). Exclusion criteria were the same as for MS participants.

Among all 129 participants of both healthy control and RRMS groups recruited in this study, most (n = 89), 68.99% were women. Male participants (n = 40) accounted for 31.01% of the sample. The ratio of female to male participants was very similar in the RRMS group (2.3:1) and the healthy control group (2.1:1). Participant ages ranged between 20 and 60 years (M = 42.33 years, SD = 9.63 years). Participants' years of education ranged between 10 to 20 years (M = 15.51 years and SD = 1.91 years). Table 5.1 depicts the statistical demographics of the RRMS group and healthy control group with the categorical variables of gender and employment status and Table 5.2 the continuous variables of age and years of education. It is clear in Tables 5.1 and 5.2 that the RRMS and healthy control groups were largely comparable in terms of gender, employment, age and years of education and therefore well matched for statistical purposes.

Sampling Procedure

Participants were enrolled utilizing a variety of methods. A trained research assistant recruited participants by approaching patients in the MS clinic waiting area and explaining the research to them. They were then given written information about the study (Appendix D) and asked if they wanted to participate. In addition, recruitment occurred by means of flyers posted in the clinic and given out by treating neurologists and clinic staff. Requests for volunteer participants, including those with RRMS and healthy controls, were also advertised on the internet. The Multiple Sclerosis Society of Canada has a research portal on their website (found by searching *msresearch.ca)* and this is visited by people with MS wanting to be involved in research. Healthy controls were also recruited through postings on Craigslist and Kajiji

Table 5.1

Descriptive Statistics of Gender and Employment Status of RRMS Group and Healthy Control Group

		RRMS Group (*n* = 79)		Healthy Control Group (*n* = 50)	
		Frequency	Percentage	Frequency	Percentage
Gender	Male	24	30.38	16	32.00
	Female	55	69.62	34	68.00
Employment Status	Employed	44	55.70	40	80
	Unemployed	35	44.30	10	20

Table 5.2

Descriptive Statistics of Continuous Variables (age, years of education) of RRMS Group and Healthy Control Group

	RRMS Group (n = 79)			Healthy Control Group (n = 50)		
	Mean	SD	95% CI	Mean	SD	95% CI
Age	42.87	9.26	[40.80 44.95]	41.46	10.21	[38.56 44.36]
Years of Education	15.51	2.21	[15.01 16.00]	15.52	1.31	[15.15 15.89]

(Appendices E and F). Potential participants were encouraged to contact the research coordinator telephonically or email. They were then supplied with necessary material about the research and a follow-up meeting were arranged with those who agreed to participate. The checklist of inclusion and exclusion criteria was completed by the researcher or trained research assistant in order to ascertain the suitability of the volunteer. If the volunteer met the criteria an appointment was scheduled for the research assessment. It is important to note that the research assistant did not score nor receive computer results of any the tests during this period and so was blind to the results during the testing session.

Instruments: Neuropsychological Assessment for Multiple Sclerosis

The assessment instruments used in this study were carefully chosen to address the aims of the research. Historically there have been a number of neuropsychological test batteries to test cognitive performance in MS. The most frequently used and most validated neuropsychological batteries are the Brief Repeatable Battery-Neuropsychology (BRB-N; Rao, 1990), the Minimal Assessment of Cognitive Functioning in Multiple Sclerosis (MACFIMS; Benedict Cookfair et al., 2006) and the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS; Langdon et al., 2012) which will all be described in detail later in the chapter and the reason for the decision to use the MACFIMS will be provided.

The most widely utilized test battery for research and clinical purposes in MS is the Brief Repeatable Battery-Neuropsychology (BRB-N). It was developed in 1990 and it has been translated and standardized in many languages (Amato, Portaccio et al., 2006; Portaccio et al., 2010; Sepulcre et al., 2006). The BRB-N is a forerunner to the continued search for shorter, valid and reliable assessments of cognitive dysfunction in MS (Hansen, et al., 2015). The battery assesses short-term and delayed verbal and visual memory, sustained attention, word

retrieval and processing speed. It includes the SDMT, the Paced Auditory Serial Attention Test (PASAT) three and two second intervals, a visuospatial test, the Spatial Recall Test 10/36 (10/36), the Word List Generation (WLG) using three letters, also known as the Controlled Oral Word Association Test (COWAT), and the Selective Reminding Test (SRT; Rao, 1990). A shorter version of the BRB-N has been used and the most sensitive tests of impairment were the (PASAT-3), the SDMT and the SRT, the verbal learning test. These tests together with the Stroop are recommended as an effective and short screening for cognitive impairment in a clinical setting (Portaccio, et al., 2009). Further research evaluating the BNB-N and the Stroop, revealed that the tests with the greatest test-retest reliability over an 18-month period were the Stroop, SDMT and PASAT (Portaccio et al., 2010). Evaluation and development of the sensitivity of tests for MS cognitive assessments is ongoing, to create neuropsychological batteries that are comprehensive, covering cognitive domains that are affected by MS, but that balance time efficiency as well. A study that compared the MACFIMS to the BRN-B, supported the choice of two different tests of visual memory and verbal learning for inclusion in the MACFIMS, because they revealed greater sensitivity in detecting specific domain functioning (Strober et al., 2009). The first was a visual memory test, the Brief Visuomotor Memory Test - Revised (BVMT-R), which was included in the MACFIMS instead of the Spatial Recall Test 10/36, which is a test used in the BRB-N. Second, when considering verbal learning and memory the CVLT 11 (MACFIMS) was more sensitive than the Selective Reminding Test (BRB-N). The MACFIMS therefore included much of Rao's (1990) original conceptualization, but replaced the Spatial Recall Test 10/36 and Selective Reminding Test. The BRB-N does not include an evaluation of executive functioning, while the MACFIMS does, namely, the Delis-Kaplan Executive Functions (D-KEFS) sorting and description tests,

and the Judgment Line of Orientation test (JLO) to assess executive problem solving, classification and visuospatial orientation functions. The BRB-N and MACFIMS take 45 and 90 minutes respectively to complete, but the latter is more comprehensive as it includes more tests.

Another commonly used neuropsychological battery for evaluating MS is the BICAMS. It is a brief cognitive screening test for use in clinical settings that was also developed to monitor cognitive function over time. It is a much shorter battery than the MACFIMS and covers essential, but limited cognitive functions. The BICAMS was created for international use to be validated and standardized in numerous languages. The three tests chosen via an expert internal panel were the SDMT, revealed as the most accurate predictor of MS cognitive dysfunction in the BRB-N and MACFIMS, the CVLT-11 and the BVMTR which are also both included in the MACFIMS. All may be given by health professionals with some training and experience in cognitive assessment (Amato et al., 2018; Benedict et al., 2012; Langdon et al., 2012). There have been numerous international studies validating the BICAMS. Research in Canada found it to be a valid measure of cognition in MS and yielded comparable results to research in other countries (Walker et al., 2016). The BICAMS was validated in a large 11 centre Italian study and found to be feasible for the identification of cognitive impairment in MS. This study also highlighted the good psychometric properties of the SDMT (Niccolai et al., 2015). A meta-analytic study of the BICAMS found that it has been validated in 11 languages and 14 individual cultures (Corfield & Langdon, 2018). The BICAMS takes 15 minutes to complete, but does not assess executive functions. It is therefore, an excellent screening battery, unlike the MACFIMS, which is a more comprehensive neuropsychological

assessment device, and further assessment is required if any test on the BICAMS is failed (Gromisch et al., 2016; Gromisch et al., 2018).

In sum, when considering the three most widely used neuropsychological batteries, the MACFIMS is the superior, more wide-ranging neuropsychological battery that encompasses cognitive domains most frequently affected by MS, not all of which are contained within the BRB-N nor the much shorter BICAMS. Consequently, in the present study the MACFIMS was used to separate the larger RRMS group into cognitively intact and cognitively impaired groups.

Development of the Minimal Assessment of Cognitive Functioning in Multiple Sclerosis

This assessment battery is regarded as a "gold standard' for testing a variety of primary functions of cognition. In 2001 an expert panel of 16 neuropsychologists and clinical psychologists from the United States, Canada, United Kingdom and Australia developed this comprehensive battery of neuropsychological tests. The intention was for the battery to be utilized both as an assessment for cognitive impairment and to monitor changes in functioning over time. Reliability, sensitivity and external validity were crucial to many tests examined by the panel (Stegen et al., 2010). Literature was also examined as part of the process to identify tests that had proven reliability and validity in the MS population. The MACFIMS is generally regarded as the most effective, comprehensive and coherent neuropsychological battery that can be conducted in a reasonable timeframe and is widely used in research. It focuses only on essential cognitive functions typically affected in MS and only uses measures for which published norms are available and have demonstrated validity and reliability (Benedict, Fischer et al., 2002). The MACFIMS has also been separately normed for the Canadian MS population confirming additional validity for the present study (Berard & Walker, 2022;

Walker et al., 2017). As a whole, the battery has been standardized specifically for the MS population. A validation study was conducted with 291 people with MS compared to a healthy control group. All of the tests in the MACFIMS significantly discriminated people with MS from healthy controls, and also, relapsing remitting from secondary progressive disease courses. Z scores were calculated for each test based on the healthy control group. Impairment was defined for a single test as a Z score < - 1.5. The standard deviation of 1.5 from the mean was, therefore, based on the norms of the constituent tests for MS in the MACFIMS battery. The validation study of this battery also established that failure on two subtests constituted cognitive impairment (Benedict, Cookfair et al., 2006; Strober et al., 2009). However, further evaluation of this test battery has revealed that certain tests in the battery such as the PASAT-2 second and PASAT-3 second versions cover the same domain. Consequently, if a test on the PASAT is failed, it is more common for research participant to fail both tests, rather than only one. If a strict compliance with failure on two tests constituting cognitive impairment was instituted, more MS participants would test as impaired than might be the case. Therefore, in the present study global impairment was taken as three failures on the 11 indices in the MACFIMS battery (Migliore et al. 2016; Migliore et al., 2017; Patel et al., 2017).

Computerized versions of the SDMT and the Stroop were included to facilitate embedded auditory distraction and to allow for wider clinical use. Worldwide there is limited access to trained neuropsychologists to assess people with MS for cognitive deficits. To address the need for timely cognitive assessment early in the disease process, validated computerized tests for people with MS allow for less specialized assessors to conduct tests, resulting in a greater number of patients assessed and screened for cognitive impairments (Akbar et al., 2011; Lapshin et al., 2013; Ruet et al., 2013; Wilkins et al., 2003). In a

comparison of traditional neuropsychological tests and a computerized screening battery, using the computerized SDMT and the computerized Stroop, the computerized battery was as sensitive as the traditional battery in detecting cognitive impairment in people with RRMS and SPMS (Papathanasious et al., 2014). The use of computerized neurological assessment devices has burgeoned over the last few years and a recent review of research identified 11 batteries, 33 individual test and 120 peer reviewed articles (Wojcik et al., 2019). A number of computerized neurological assessment devices were identified as valid to screen for MS-related cognitive dysfunction. All of the tests used in the present study which are computerized, were mentioned in the review, namely the SDMT, Stroop and PASAT 2 and 3. Computerized tests are simple to administer, are inherently tester standardized, and minimize the manual dexterity required for pencil and paper tests. Reaction times can be automatically recorded by computer, resulting in greater accuracy in timing precision. The tester scores the errors separately.

Visual Acuity and Colour Recognition

Visual acuity was tested with a Snellen chart. This chart was developed in 1862 by Dr. Hermann Snellen and is a standard instrument for use in visual acuity examinations. It contains 11 rows of capital letters decreasing in size with each row. It was essential that visual acuity be equal to or better than 20/70 corrected in both eyes. Colour recognition was also tested prior to the assessment to ascertain that the participant was able to discriminate a full range of colours, which was necessary for the Stroop test. Participants were excluded if these screening tests were not passed.

Cognitive assessments

The ramifications of cognitive deficits have extensive outcomes and the continued development of precise, neuropsychometric tests is essential to reveal cognitive status. As mentioned previously, the tests developed to date span comprehensive batteries like the MACFIMS (Benedict, Fischer et al., 2002), to more concise tests such as the BRB-N (Rao, 1990) and the even shorter BICAMS (Benedict et al., 2012; Langdon, 2012). Psychometric data supports all three assessment batteries, however, time constraints have propelled the exploration for even shorter measures of cognition that are sensitive, valid and reliable. As discussed in the literature review, the SDMT (Smith, 2002) has become the test of choice, with the suggestion that it replace the PASAT (Gronwald, 1977), which has been a test often used to assess speed of information processing, sustained and selective attention (Drake et al., 2010). The Stroop Colour-Word Interference Test (the Stroop) is frequently utilized in MS assessments and was included as an associate evaluation to the SDMT. Both the Stroop and SDMT assess information processing speed and are known as rapid serial processing tests (Hughes et al., 2013)

Wechsler Test of Adult Reading

The Wechsler Test of Adult Reading (WTAR) is a neuropsychological test developed to determine premorbid intellectual function before the onset of disease. It is regarded as a 'hold' test reflecting an individual's past level of cognitive functioning (Groth-Marnat & Wright, 2016). It is an important measure to quantify the impact of brain impairment, by comparing premorbid IQ to current cognitive functioning and has been shown to be valid with high test-retest reliability (Green, et al., 2008). It was included in this study in order to match the MS and control groups on intellectual ability to ensure between group equivalency.

When the WTAR was developed in 2001, it was standardized with the Wechsler Adult Intelligence Scale and Wechsler Memory Scale and is the only reading test to be normed in this way. WTAR scores correlate significantly with verbal IQ (r = .75), verbal comprehension (r = .74) and full-scale IQ (r = .73; Wechsler, 2001). The test has been utilized in MS cognitive studies, which took reading ability into account (Romero et al., 2015; Sandry & Sumowski, 2014; Sumowski et al., 2009). The test is based on reading recognition and pronunciation of irregular English words that are not phonetic. However, it does not require knowledge of the meaning of the words, but relies on previous learning of the pronunciation of the words. Reading ability is virtually unaffected by cognitive decline associated with neurological damage that is not severe (Wechsler, 2001). People with RRMS have mild brain damage and WTAR scores can provide insight into the extent of their cognitive reserve. High cognitive reserve, which is known to be protective in the context of an acquired brain disease, is related to higher premorbid intellectual functioning, as well as number of years of education and involvement in intellectual pursuits (Benedict et al., 2011; Feinstein et al., 2013; Scarpazza et al., 2013; Schwartz et al., 2013; Sumowsk et al., 2009; Sumowski & Leavitt, 2013). Individuals with higher cognitive reserve can withstand more neurological damage before manifesting cognitive impairment (McNicholas et al., 2018). By extension, higher cognitive reserve may attenuate the effects of auditory distraction on processing speed and it was essential, therefore, to control for this variable in the present study.

Minimal Assessment of Cognitive Functioning in Multiple Sclerosis (MACFIMS)

The MACFIMS consists of 11 tests that assess seven cognitive domains commonly affected and resulting in cognitive dysfunction in people with MS. These are information processing speed, verbal and visual learning, memory, working memory, executive function,

visuospatial processing and verbal fluency (Hansen & Lautenbacher, 2017). The tests take 90 minutes to complete and have been normed for the English-speaking MS population in the United Kingdom, USA, Canada and Australia (Benedict, Fischer et al., 2002; Benedict et al., 2006; Langdon et al., 2012; Parmenter et al., 2010; Stegen et al., 2010). By convention, failure on each test of the MACFIMS is defined as a score 1.5 standard deviations or greater below the normed values established in the original MACFIMS validation research (Benedict, Cookfair et al., 2006). The exception is the SDMT score which is measured in time (in seconds) taken to complete the test. In order to remain consistent with respect to determining the threshold for impairment, a score of 1.5 standard deviations and greater beyond the mean score of the control group was deemed as a failure. This standard deviation from the mean of the healthy controls is routinely used for the SDMT in MS research (Benedict, 2002; Sumowski et al., 2018). The comparative norms for the SDMT were obtained from the healthy controls in the 2006 validation study (Benedict, Cookfair et al., 2006). However, in the current study, data was collected from a healthy control group that was carefully matched to the MS group, which was used for comparison. As previously noted, global impairment was designated as failure on three or more cognitive measures.

Given that the SDMT was performing two roles, that is, part of the MACFIMS and central to the hypotheses, it was prudent to analyze the MACFIMS data with and without the SDMT in detecting global impairment. Therefore, global impairment was analyzed statistically as three out of the 11 indices falling 1.5 SD below the mean of the control group, a standard cutoff with the SDMT and failure of three out of ten indices, with the exclusion of the SDMT[20] (Sumowski et al., 2018). It followed that the numbers in the intact and impaired RRMS groups

[20] The use of this cutoff, named Criterion 2, will be described in the Results Chapter

changed based on the two criteria of global impairment. The two groups were then analyzed to assess the possible confounding of the dual role of the SDMT.

The MACFIMS includes 11 indices derived from seven tests, namely, the Symbol Digits Modalities Test (SDMT), the Paced Auditory Serial Addition Task (PASAT-2 and PASAT-3 second versions), the California Verbal Learning Test-11 (CVLT-11), immediate and delayed recall, the Brief Visuospatial Memory Test-Revised (BVMT-R), immediate and delayed, the Delis-Kaplan Executive Functioning System(D-KEFS) including two categories, verbal and spatial, the Judgment of Line Orientation Test (JLO) and the Controlled Oral Word Association test (COWAT). These tests will briefly be described.

The California Verbal Learning Test – 11 (CVLT-11) (immediate and delayed*)*

This test assesses the manner in which test participants approach and develop strategies in the learning and memorizing of verbal material (Delis et al., 2000). The test consists of both an immediate total recall trial and a delayed recall trial of exposure to new material. The normative database was derived from a standardized sample of 1.087 people aged 16-89 years (mean age = 47.74; SD = 22.87). The split-half and coefficient alpha lay in the moderate to high range r = .80. The authors reported a reliability of r = .84 after a year with 21 retested participants (Delis et al., 2001a). The adult version was normed for neurologically intact people aged 16-89 years (mean age = 58.93, *SD* = 15.35: education level (mean = 13.83, *SD* = 2.70), (Delis et al., 2000). The CVLT-11 is used extensively in psychological batteries for MS (Beier et al., 2019; Langdon et al., 2012). It has been validated and found to be reliable for the MS population in a study with 351 people with MS and 69 matched controls all 18 years and older and fluent English-speakers (Stegen et al., 2010). Construct and external validity were statistically supported. This test is included in the BICAMS and MACFIMS.

Participants listened to a list of 16 words (List A) over five trials. Each trial consisted of reading the list and then writing down recalled words, which could be presented in any order. The words were from four different semantic categories, however the words from each category were not presented consecutively. The cumulative number of correct words remembered for each of these five administrations was noted. List B containing 16 words was presented once after the five trails as an interference list. Then list A had to be recalled. For the delayed recall, twenty minutes after the initial administration the participant was requested to name as many words they could remembered from List A. The number of correct responses was recording by the tester for immediate and then delayed times. For statistical purposes the score for immediate recall was the cumulative number of correct list word over five trials and for delayed recall the total number of responses for the one recall trial administered after 20 minutes.

The Brief Visuospatial Memory Test (BVMT-R) – Revised (immediate and delayed)

This test consists of immediate and delayed recall of exposure to new visuospatial material. Developed and revised by Benedict and Groninger (1996), the test was modeled after the Visual Reproduction subtest of the Wechsler Memory Scales (Weschler, 1997). These authors completed a standardization study to investigate reliability and validity of the BVMT-R and reported a sensitivity of 98% and a specificity of 82%. It was found to be a valid and reliable test of learning and remembering simple geometric designs (Benedict et al., 1996; Benedict, 1997). The test is regularly used in assessing visuospatial memory in MS and is included in the BICAMS and MACFIMS (Tam & Schmitter-Edgecombe, 2013).

Participants were presented with a display of six abstract visual designs in a two by three matrix for ten seconds. The display was taken away and participants were requested to draw the shapes from memory as precisely as possible and place them in the same space on the page as the original display. Three learning trials were administered. The drawings for every trial were scored based both on the similarity of the drawing and the location on the page. These scores were then added for a total recall score. Twenty-five minutes after the first presentation of the figures the participants were requested to draw the designs in the correct place from memory. These were then scored for delayed recall.

Delis-Kaplan Executive Functioning System (D-KEFS), two categories

The D-KEFS assesses executive functioning in the areas of problem-solving, verbal and spatial concept formation, and flexibility in thinking. There are nine sub-tests, which assess flexibility of thinking, problem-solving, ability to categorize, think abstractly and reason (Delis, 2001b). The D-KEFS Sorting test was chosen as one of the subtests of the MACFIMS.

The D-KEFS was the initial battery of executive tests that was co-normed on a significant test group with separate normative scores for each test, which allowed them to be used separately (Homack et al., 2005). The D-KEFS standardization study consisted of 1750 participants between the ages of 8-89 and was divided onto 16 age groups. Raw scores on the tests were found to be normally distributed. Test-retest correlation for the D-KEFS Sorting test was in the moderate range, $r = .60$ and internal consistency for the age range of participants in the present study was $r = .77$ (Delis et al., 2001b). The D-KEFS Sorting test was based on the California Card Sorting Test (CCST) developed by Delis in 1988 and in earlier research the CCST was administered to MS participants and they performed more poorly than controls both in terms of sort categories and explanations (Beatty & Monson, 1996; Delis et al., 2001a).

Following the development of the D-KEFS battery, the validity of the D-KEFS Sorting test was evaluated in 111 patients with MS and 46 matched controls and found to be a better discriminative test of executive tasks and consequent cognitive impairment than other card sort test for people with MS. Good validity was established in this study (Heled et al., 2012; Parmenter et al., 2007).

The D-KEFS Sorting test contains two sets of six stimulus cards each with a different shape and a single word printed in the centre. Each set has eight pairs of possible arrangements or sorts (five perceptual concepts and three verbal concepts). It is a two-part card-sorting test whereby participants were requested to sort the six cards into two groups of three cards in as many ways as possible ways involving at least eight varying categories, for example, card shape, card colour, semantic connection between words, amongst others and then explain the rationale behind the decisions. The two half-tests are independent but equivalent (Delis et al., 2004; Heled et al., 2012). Four minutes were allowed for each of the card sets. The test was scored corresponding to the number of accurate sorts and the descriptions given by the participants rated in terms of abstractness and precision of the sort descriptions according to a template.

Judgment of Line Orientation test (JLO)

This test assesses visuospatial processing and tests the ability to estimate angular relationships in space. The test developed by Benton et al. in 1978, and requires participants to distinguish the orientation or slope of two lines exhibited on paper. The original study was conducted on a control group of 144 people equally divided between females and males. The split-half reliability was $r = .91$ (standard error = 1.7) and the test-retest reliability coefficient was $r = .90$ (standard error =1.8) (Benton et al., 1978). Reliability was reported as $r = .84$ in

128 young adults (mean age = 21.5 years, SD = 4.4) and r = .81 in a group of older adults (mean = 66.3 years, SD=6.9), revealing good reliability and consistency over age ranges (Spencer et al., 2013). The internal consistency was reported as high at .90 (Benton et al., 1994; Lezak et al., 2004).

The test contains 30 items with each presenting a dissimilar pair of angled lines, which had to be matched to the given legend. There is the choice of 11 different orientations lines and participants had to identify and provide a number corresponding to each orientation and match a line in the legend that was provided to them. The number of correct answers was scored out of 30 and corrected for age and gender, representing the raw score data (Benton et al., 1994).

The Controlled Oral Word Association Test (COWAT)

This test was developed by Benton and colleagues (Benton et al., 1994) and assesses verbal fluency and retrieval. In 1996 the reliability of the COWAT was re-assessed with a sample of 360 participants aged 16-70 years. A coefficient alpha of α = .83 was found and test-retest reliability was r = .74 (Ruff et al., 1996). Good reliability and construct validity have consistently been found in numerous studies, too many to cite in the scope of this study (Strauss et al., 2006). The letters used in the present research were FAS, which are the most commonly used letters and this version continues to be the most widely used test of verbal fluency (Benton et al., 1994; Groth-Marnat & Wright, 2016; Ross et al., 2006). The criterion validity of the above four tests of the MACFIMS including the COWAT and sensitivity of 90.9% and a specificity of 90.5% was obtained (Gromisch, et al., 2016)

The three trials in this test were successive, each of one-minute duration. Each trial began with a different designated letter of the alphabet. Participants were asked to

spontaneously generate as many novel words as possible within the time limit. The instructions emphasized that proper nouns could not be included, nor could the same words with different endings. The cumulative total on each of the three trials constituted the score.

The Paced Auditory Serial Addition Task (PASAT-2) and (PASAT-3) second intervals

The PASAT is a rapid serial processing task, which is a serial-addition task that measures working memory specifically and also speed of information processing, sustained and divided attention, interference suppression and concentration in people with MS (Nagels et al., 2005). The PASAT is extensively used and has been succinctly described as a test that measures cognitive effort, by means of information processing speed and concentration, during a high demand attentional task (Matias-Guiu et al., 2018).

Developed by Gronwall in 1977, the PASAT consists of two separate trials. The PASAT-3 is the three second version and trial two, PASAT-2, is the second version. Psychometric results show high internal consistency and test-retest reliability (Tombaugh, 2006). The PASAT's split-half reliability is about .9, revealing a high internal reliability and Cronbach's alpha is reported as $\alpha = .90$. Test-retest correlations are greater than .9 (Strauss et al., 2006). When used as a cognitive screen with 127 MS patients, the test had an individual sensitivity of 49.06% and specificity of 84.93% which increased when results were used in a composite battery (Hansen et. al., 2015). Results of an MS study revealed that reduced information-processing speed resulted in lower timed scores compared to healthy controls (Forn et al., 2008). The PASAT yielded a sensitivity of 74% and a specificity of 65% in discriminating cognitive impairment in RRMS (Rosti et al., 2007). Cognitive research on 237 RRMS patients and 57 healthy controls evaluated the efficacy of the PASAT-3. The PASAT-

3 had a sensitivity of 73% and a specificity of 64% in concordance with findings of the previous study (Lopez-Gongora et al., 2015).

The test is computerized and prerecorded. A sequence of 60 numbers spanning 1 to 9 were presented at a fixed rate in the auditory modality with the numbers ranging from 1 to 9 at intervals of two or three seconds depending on the trial. Participants were asked to add the number they heard to the previous number and not to give the cumulative total of the previous two numbers. The answer was given orally. For example, if the first two numbers are "3" and "8" the answer is "11". If the next number is "5" it is added to the previous number heard which is "8" and the answer will be "13" and so on until the 60 numbers are completed. There were practice trials of a few numbers beforehand so that the concept could be grasped. The second trial increased processing demands as the numbers were only separated by two seconds. The number of correct answers corrected for education attainment in years was recorded as the score.

The Symbol Digits Modality Test – computerized (c-SDMT)

This test assesses speed of information processing in the visual modality, tapping into scanning and tracking aspects of attention and is regarded as a rapid serial process task. The SDMT was originally developed by Smith in 1982 to screen for cognitive dysfunction (Smith, 2002). The test involves substituting geometric designs for numbers in either an oral or written format. The test was originally normed on 1,307 cognitively intact adults with an age range of 18 – 78. Studies have revealed that a cutoff score of 1.5 SD below the mean for each of the six age groups normed, resulted in correct classification of 92% of control adults tested. Therefore, it is accepted that scores that fall at or below 1.5 SD from the mean for any given age indicate cognitive dysfunction.

The test-retest reliability of the SDMT was r = .80 for the written form and r = .76 for the oral version (Smith 2002). Research conducted on four alternate forms of the SDMT using the same symbols, but with different number pairings revealed test-retest reliability with r values greater than .80 (Benedict et al., 2012). The study did not fully overcome practice effects, which was the reason for using a counterbalance methodology in the present study (Benedict et al., 2008).

In the MS population the validity of the SDMT was assessed in 400 people and was found to be sensitive to cognitive decline. In fact, the SDMT was deemed more sensitive than other tests at detecting cognitive impairment in the early stages of MS and in aiding the diagnosis of RRMS (Brochet et al., 2008). The construct validity of the SDMT in 278 MS participants confirmed the high sensitivity of the test to cognitive impairment, also that it was the best predictor of cognitive decline over time. It is the test that most frequently discriminates MS from control groups as well as the psychometric test that significantly correlates cognitive dysfunction with MRI measures of atrophy, lesion burden and micro brain pathology (Benedict, DeLuca, Phillips et al., 2017). A number of studies over the last two decades have indicated that the most reliable and valid single assessment tool for general cognition is the SDMT (Benedict et al., 2012; Brochet et al., 2008; Drake et al., 2010; Gromisch et al., 2018; Parmenter, Weinstock-Guttmann, et al., 2007; Sheridan, et al., 2006; Sonder et al., 2013; Vogel et al., 2013). Additionally, the SDMT showed consistency over repeated testing in people with MS (Benedict et al., 2008). It is the most sensitive test at assessing cognitive deficits in both the MACFIMS and the BRB-N battery (Benedict et al., 2008; Strober et al., 2009). The SDMT is regarded as a ‘sentinel’ test for cognitive impairment in MS, since it outperformed most tests with a specificity of 60% and a sensitivity of 91% (van Schependom et al., 2014). It is the only

test that is common to all recommended cognitive neuropsychological batteries for people with MS and measures important change over time (Benedict et al., 2017; Strober et al., 2019). The International Multiple Sclerosis Cognition Society has recommended that the SDMT test be used as a minimal baseline test to screen for cognitive impairment and then to have an annual reassessment with the same instrument to detect acute disease activity and to assess for new cognitive problems or deterioration (Kalb, et al., 2018). It is an easy and time-efficient test that can be used to detect and screen for cognitive impairment in clinical practice. If impairment is found on the test, this will alert the treating practitioner to cognitive problems which may be observed over time and, if necessary, followed up with a fuller neuropsychological assessment and remedial treatment.

The present study was an endeavour to augment the sensitivity of the SDMT in detecting cognitive deficits by the introduction of real-world distractors into the test administration. In order to ensure standard administration of the auditory distractions, it was necessary to use a computer administered version of the SDMT. The c-SDMT is a computerized version of the original SDMT (Smith, 1982). The test-retest reliability of the cSDMT in MS patients was found to have an interclass correlation coefficient (ICC) = .97 (Wojcik et al., 2019).

Computer-assisted assessment is frequently used in psychological practice and has grown significantly over the last 40 years. Computerized tests save on professional time, control for tester bias and consequently can increase test-retest reliability (Groth-Marnat & Wright, 2016; Wilken et al., 2003). Computerized versions of tests have been developed for the MS population as such these tests can be implemented when a person is undergoing a fMRI (Smith et al., 2012). The computerized version of the SDMT was validated for use with people

with MS with a sample of 119 MS participants and 38 controls (Akbar et al., 2011). Both groups completed the SDMT using the paper version and the computerized version. Both versions revealed significant differences between controls and MS participants with the latter performing more poorly. The computerized version of the SDMT appeared to reduce the reliance on head motion and eye tracking movements in both groups compared to the paper and pencil version suggesting a more accurate portrayal of information processing performance. This meant that for people with MS the motor component, such as motor and eye tracking movements, which is often compromised, was eliminated and a potential confounder was controlled. The c-SDMT was found to have sensitivity of 71% and specificity of 84% in differentiating between people with MS and healthy controls. Good test-retest reliability on this test was found (ICC = .94). The c-SDMT has since been used as part of the MACFIMS (Lapshin et al., 2013).

In the present study the SDMT test comprised nine boxes in a row with a symbol in each box. Below this row was an identical row of nine boxes with numbers 1 to 9 displayed, corresponding to a different symbol above it. Below this legend were the same nine symbols in a different order in nine boxes (Figure 5.2). In the study the participant verbalized the number corresponding to each symbol. Instructions were given to finish the test as quickly as possible. A practice run of nine symbols was first administered, thereafter, the test consisted of eight trials. At the end of each trial the tester pushed the space bar to initiate the next trial. The time taken for each trial was recorded by the computer and the tester recorded the number of errors made per trial. A total time for the eight trials was summed and a mean was also computed.

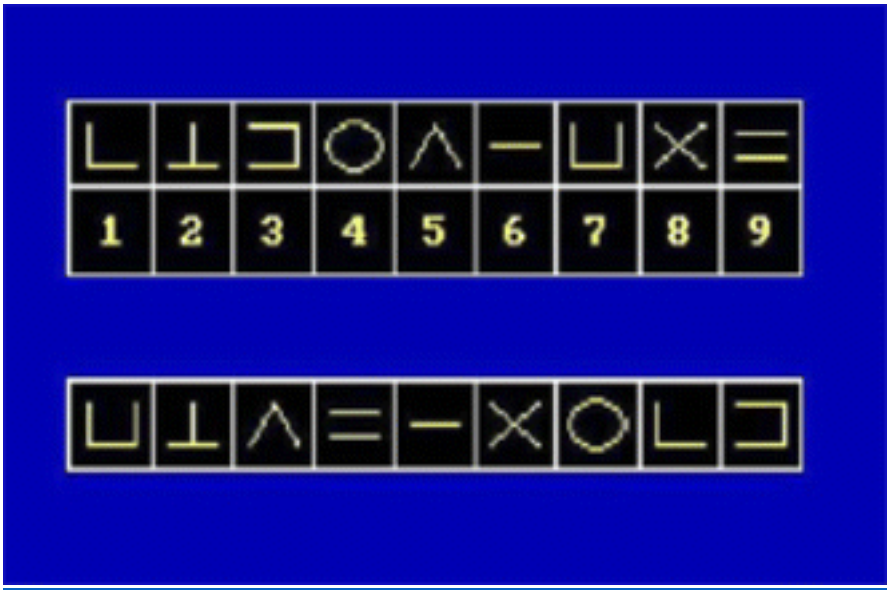


Figure 5.2

Screen shot of the computerized Symbol Digits Modalities Test (Akbar, Honarmand, Kou & Feinstein, 2011)

The Stroop Colour-Word Test (the Stroop)

The Stroop Colour-Word test assesses interference in reaction time and is a rapid series processing task. Impairment on this test is related to deficits in selective attention and processing speed (Lezak et al., 2004) The reason for choosing the Stroop is that the test is used to assess the ability to inhibit cognitive interference (Scarpina & Tagini, 2017). This occurs when a specific feature impedes the processing of a second feature. In the case of the Stroop there is inherently a distractor element as colour recognition potentially impedes reading coloured words. Differences in reaction times suggest that either speed of processing is the source of variance or that it is the inability to inhibit the distractor stimulus (Wilson et al., 2016). In MS decrease in speed of information processing in performance on the Stroop, rather than colour difficulty and interference was found to be a predominant feature (Bodling, et al.,

2008; Denny & Lynch, 2009). The Stroop is sensitive to impaired concentration and attention, which results in problems in processing distractions (Lezak et al., 2004). MS participants presented with the computerized Stroop (colour-word, third trial) exhibited slower processing speed which resulted in greater reaction time (MacNiven et al., 2008). Morrow (2013) collected normative data for the Stroop on a healthy English-speaking Canadian population. She then compared people with MS to the normative data and found that in addition to processing speed the predominant cognitive domain affected in MS was selective attention. She also found that the Stroop and SDMT were independent tests of selective attention and processing speed. In the present study the Stroop, without distractors, tested the inhibitory functions of the participants, the unintelligible speech distractors added a further layer of distraction requiring increased inhibition of cognitive interference.

In the Stroop, the testee is required to attend to one characteristic of a stimulus, but ignore another one at the same time. Colour naming can be slowed by the competing information of the colour of the ink, which may be the same or is different to that of the word. Automatic reading must be inhibited to name a colour (Lueng et al., 2000). The brain takes longer to react to recognizing colours than words, therefore, reaction time and processing speed are impacted by the discrimination between colour recognition and coloured words.

The Stroop used in the current research was a computerized iteration of the original Stroop (Stroop, 1935). The total time to finish the test was recorded by the computer. The test entailed three trials. In the first, the participant read a list of colour names. In the second trial, coloured squares were presented on the screen and participants named the colours. In the third trial, the participant was provided with the names of colours typed in colours that did not match the word and was required to name the colour, not read the written word. Responses were given

orally and errors were recorded by the tester, who began and ended each trial by striking the space bar. The raw score was based on the time to complete the colour distraction task. It is important to note that the distractors were only embedded in the third trial, namely, the full Stroop paradigm. This reflected the fact that the first two trials, namely, reading speed and speed of colour identification were control trials and are not sensitive markers of information processing speed, consistent with previous MS research (Denney & Lynch, 2009). Figure 5.3 is a screenshot of the colours of the words that were used in this traditional version of the Stroop, namely, blue, red, green and yellow.



Figure 5.3

Screen shot of the computerized Stroop Colour-Word Association test

Rapid Serial Processing Tests in Multiple Sclerosis

Traditionally there have been three rapid serial processing tests most commonly used for assessing deficits in information processing speed, which is cited as the principle cognitive impairment in MS; the PASAT, SDMT and Stroop (Amato, Portaccio et al., 2006; Bodling et al., 2008; Hughes et al., 2013; Matias-Guiu et al., 2018). Items in serial processing tests are presented sequentially with little variation in operational requirements. The tests must be performed as quickly as possible within a certain time frame. Having to carry out the operation many times in the given period aggregates small individual differences in information processing and enhances the sensitivity of these measures at differentiating people with MS from healthy controls (Denney & Lynch, 2009; Fuchs et al., 2022; Parmenter, Weinstock-Guttman, et al., 2007). The three composite batteries for assessing cognitive impairment in MS (the BRB-N, the MACFIMS and the BICAMS), have utilized the PASAT and SDMT. The BRB-N and the MACFIMS both include the SDMT and PASAT to primarily assess information processing speed and attention. However, the BICAMS, as a briefer test uses only the SDMT to assess information processing speed. The Stroop and the SDMT are based on time taken to complete the test, are self-paced with the instruction that the participant work as quickly as possible. Generally, few errors are made as the tests are not difficult. On the other hand, the PASAT is more cognitively taxing as executive skills are required in terms of inhibition or interference suppression, and significant working memory and arithmetic skills are utilized. A number of MS participants in studies do not complete the test as it associated with stress and agitation and because it so fast-paced missing values are often reported in studies (Lopez-Gongora et al., 2015). Additionally, research suggests that the SDMT replace the PASAT in the Multiple Sclerosis Functional Composite (MSFC), a diagnostic assessment

of MS, for the reasons outlined above (Brochet et al., 2008; Lopez-Gongora et al., 2015). The SDMT is reported to have better test-retest reliability and increased ability to discriminate healthy controls from MS participants (Drake et al., 2010). Therefore, the SDMT and the Stroop were chosen in the present study as they were likely to be well tolerated and completed in test batteries. The computerized form of the tests required only verbal responses. Thus, the possible confounding factor of physical hand dexterity was removed. Both tests have some cognitive burden in that the third trial of the Stroop, which was used in the present study, requires the executive function of suppression or inhibition of automatic reading in order to name the colour, and the SDMT requires changes in visual focus between the target item and reference key.

The following section addresses the type of embedded auditory distractors added to both the SDMT and Stroop. It was hypothesized that these distractors would further slow processing speed, thus enhancing the ability of these tests to detect a primary deficit in cognition, namely, processing speed in people with MS.

Distractor versions of the Symbol Digits Modalities Test and Stroop Colour-Word Association test

The auditory distractor that was embedded in the tests took the form of unintelligible speech. The sound had the acoustic properties of speech with change in pitch and cadence and the abrupt sound sequences that are characteristic of English. Individual words were not identifiable in order to recreate a generic background unintelligible speech environment (Beaman & Holt, 2007). The unintelligible speech stream was generated from a scripted conversation between a male and female and was embedded in the computerized tests. In the SDMT, the unintelligible speech ran for the duration of the test. In the case of the Stroop, the

unintelligible speech ran for the duration of the third trial only, namely the colour-word interference task. Participants' scores on the distractor tests were compared to their scores on the non-distractor counterparts.

The Hospital Anxiety and Depression Scale (HADS)

Self-report mental health questionnaires are frequently used in research as they capture a range of important psychiatric symptoms. Since access to expert psychiatric diagnoses in MS research settings is most often not available, these questionnaires fill a vital gap (Boeschoten et al., 2016). The initial HAD study found strong positive correlations between the clinical psychiatric diagnoses of 100 patients with depression and general anxiety disorder and the same participants' scores on the HADS (depression r =.70, and anxiety r =.74, with $p < .0001$; Zigmond & Snaith, 1983). Significant levels of anxiety and depression are highly prevalent in people with MS (Jones et al., 2012). Clinically significant depression affects 25% to 50% of people with MS over a lifetime, which is three times the rate of the general population (Feinstein, 2011). In the general population 8.5% of people experience a generalized anxiety disorder whereas in the MS population the prevalence is approximately 22% (Filser et al., 2022; Marrie et al. 2015).

Both anxiety and depression have an impact on cognition and clinicians are frequently confronted with the challenge to separate whether and to what extent mood and anxiety influence impairment in cognition. There is comorbidity of depression and anxiety in approximately 20% of people with MS (Leavitt et al., 2020). However, when looking for comparative numbers in the MS literature there are large disparities in the reporting of prevalence rates for depression and anxiety. To address this problem two metanalytic studies of depression and anxiety in MS were undertaken. In the first study, 118 studies were included.

The summative prevalence of anxiety was 21.9% and the summative prevalence of depression was 23.7% (Marrie et al., 2015; Marrie et al., 2018). In the second metanalytic study 58 articles were included encompassing a total sample size of 87,756 people with MS. The pooled mean prevalence was 30% for depression, slightly higher than the previous study, and 22.2% for anxiety, similar to the previous study. Research on depression outnumbers those of anxiety by four to one (Boeschoten et al., 2016; Wallis et al., 2020).

Numerous studies have been conducted to assess the impact of depression and anxiety on cognition in people with MS. Anxiety and depression in people with MS were assessed over three years using the HADS as the diagnostic measure. Results in those experiencing both anxiety and depression revealed a decline in information processing speed (Marrie et al., 2021). However, in contrast to other studies, 60% of participants had comorbid anxiety and depression, but these were not significantly correlated with either processing speed nor verbal learning (Vissicchio et al., 2019). It is difficult to deconstruct to what extent anxiety and depression contribute to cognitive impairment, although some impact is acknowledged (Wallis et al., 2020). Whitehouse et al. (2019) found that anxiety negatively affected performance on verbal learning, information processing and memory, whereas depression reduced performance only on information processing speed. In two independent samples anxiety and depression were linked to different cognitive functions (Demarree et al., 2003; Whitehouse et al., 2019). Anxiety was related to non-verbal memory and depression was related to attention and processing speed (Leavitt et al., 2020). People with MS completed the HADS and MACFIMS in a study comprising 151 participants experiencing mild to moderate symptoms of MS. Depression was associated with impairment on the SDMT, CVLT-11, BVMT-R - delayed recall and the D-KEFS. Anxiety was correlated with impairment on the PASAT, BVMT-R -

immediate recall and delayed recall tests (Morrow et al., 2016; Skorve et al., 2020). In contrast, 322 people with MS were assessed on the impact of anxiety, depression and stress on cognitive functioning. Anxiety was particularly potent as a significant predictor of cognitive performance and was found to have far stronger predictive power than depression. Anxiety particularly impacted memory and word fluency, complex attention and information processing speed (Goretti et al., 2014; Ribbons et al., 2017). Anxiety also affected performance on the SDMT and PASAT -2 and -3, thus revealing deficits in information processing speed and working memory (Goretti et al., 2014; Leavitt et al., 2020). This result reveals that anxiety affects cognition by impacting attention, which in turn slows information processing speed. Anxiety scores based on the HADS, which may be particularly high in some cases, affected verbal learning as assessed on the CVLT-11 and information processing speed based on the SDMT (Vissicchio et al., 2019; Jones et al., 2012; Marrie et al. 2021).

Depression in people with MS was associated with impaired performance on the SDMT, BMVT-R delayed recall and DKEFS, revealing impaired verbal and visuospatial memory, sustained attention and information processing speed (Leavitt et al., 2020; Morrow et al., 2016; Nunnari et al., 2015). Difficulties in executive functioning and working memory have also been found (Feinstein et al., 2014). As is evident in the above studies, there is disagreement concerning the particular cognitive spheres affected by depression and anxiety, however, the deficits that consistently stand out are in speed of information processing, verbal and non-verbal learning, memory, attention, working memory, executive functioning and word fluency, all cognitive domains tapped into by the MACFIMS.

For the purposes of the present study people with RRMS were singled out from other disease courses, yet few studies explore the effects of anxiety and depression on cognitive

deficits in this disease course. In a study targeting people with RRMS two cohorts were studied, the first contained a group averaging 2.2 years from diagnosis, and the second an average of 7.6 years from diagnosis. In both cohorts, anxiety was related to impairment in non-verbal memory and depression was related to deficits in attention and processing speed. Additionally, lesion volume did not account for the relationship of anxiety and depression to cognitive function (Leavitt et al., 2020). In order to investigate the prevalence of depression and anxiety in the different courses of MS a metanalytic review was conducted on recent data between the years 2015-2021 (Peres et al., 2022). Twelve studies met stringent inclusion and exclusion criteria. A subgroup analysis was performed to extract data based on the different MS disease courses. However, the study was only able to discern three out of the twelve studies that evaluated different MS subtypes. The most commonly used scale was the HADS and the overall prevalence of depression in people with RRMS was 15.8% and for anxiety it was 21.4%. These percentages were lower than those of the more progressive forms of MS. Depression is less common early in MS than in the later and more progressive stages, and those with more severe depression have greater difficulties in executive functioning, speed of information processing and working memory (Feinstein et al., 2014). There is limited information available on the role anxiety plays in cognitive impairment particularly regarding the different disease courses, although it is known that anxiety impacts cognition (Morrow et al., 2016; Vissicchio et al., 2019). In a seminal study evaluating the impact of anxiety on cognitive impairment, 190 people with RRMS were included. Forty percent of the participants tested as cognitively impaired on the BRB-R. The tests most frequently failed were the SDMT, the PASAT 3 and 2 and the verbal memory subtest on the BRB-R, the SRT (Selective Reminding Test; Marrie et al., 2021).

Since cognitive impairment occurs in the absence of depression it is likely that depression exacerbates existing cognitive difficulties rather than causes them. This is the reason apart from general well-being and quality of life that depression be treated. In the current study both depression and anxiety, as revealed on the HADS, were found in the MS sample and with strong research evidence of these covariates confounding results, this possibility was investigated in the statistical analyses.

The HADS has been validated for the MS population and a cutoff score of 8 or more on the HADS depression subscale resulted in sensitivity of 90% and specificity of 87.3%. The same cutoff for the anxiety subscale provided sensitivity of 88.5% and specificity of 80.7 % (Honarmand & Feinstein, 2009; Marrie et al., 2018). The HADS self-report scale contains 14 items (seven each for depression and anxiety) enquiring about mood and anxiety state in the week prior to testing. Each item was answered on a 0-3 scale for a total of 21 points for each subscale and had a cut-off score of 8 on the two subscales. Scores of eight and above indicated clinically significant depression and anxiety.

Pilot Study

In order to ensure that the performance of the healthy controls did not fall into the impaired range when distractors were added, a pilot study was conducted on ten healthy controls between the ages of 18-60 utilizing the inclusion and exclusion criteria detailed in the sampling section. The addition of distractors to the SDMT and the Stroop test did not push the healthy control data beyond the cut-off thresholds for impairment (that is 1.5 SD above or below their combined means scores) or below the threshold for impairment on the MACFIMS. One control participant tested as cognitively impaired with three or more failures on the MACFIMS. Since the cognitive battery is challenging it is accepted that there will be a small

number of controls, as representative members of the general population, who may test as impaired following a normal distribution of cognitive ability. Adhering to the same protocol, healthy controls were matched to RRMS participants. The inclusion criteria included falling between ages 18-60 years. In the case of RRMS participants, each had to have clinically definite MS and in the case of controls not have MS (hence named healthy controls). Exclusion criteria, which were applied to both groups have been detailed in the sample section. In MS literature control participants are not pretested for cognitive ability, but must be matched on age, gender, years of education and in some cases for greater robustness premorbid IQ. A literature search did not yield studies in which cognitive intactness of the control group was addressed, nor were controls tested *a priori* for intact cognition. (Akbar et al., 2011; Benedict et al., 2008; Drake et al., 2007; Grossi et al., 2020; Lapshin et al., 2013; Migliore et al., 2016; Drake et al., 2010). The present study therefore, followed the precedent of the MS research literature.

Procedure

Testing took place in an outpatient MS hospital clinic in Toronto, which is part of the health/science network of the University of Toronto. It is a teaching hospital and research is routinely conducted in the Multiple Sclerosis Clinic, which services approximately 2,000 MS patients.

Face-to-face testing of each individual took place on a separate non-clinic day in a private office and was completed on average in two-and-a-half to three hours. At any point in the process participants could request a break, but this was rarely required due to natural breaks between the tests. The assessor was a trained and experienced research assistant. A consent form was provided to participants prior to the research (Appendix B). All aspects of the

research were fully explained to the participant and the consent form was signed by the participant and researcher. Demographic questionnaires were given to healthy controls and MS participants prior to the commencement of the cognitive assessment (Appendix C). Information was collected regarding gender, years of education, languages spoken, employment/occupation, source of income if not employed, and marital status. Multiple sclerosis neurological data was obtained from the patient's neurologist and included the course of MS, illness duration, and the expanded disability status score (EDSS). A neurologist was the only practitioner who was permitted to provide this score for the research as it was necessary that a highly skilled physician make the diagnosis for the disability score, as well as for the course of the disease, RRMS.

Order of testing

Visual acuity and colour blindness were tested first. If both were passed, the rest of the assessment proceeded. The WTAR was the next test administered. In order to control for possible practice effects, as the two versions of the SDMT and Stroop were completed twice within a three-hour period both with and without distractors, a counterbalanced methodology was implemented. The focus of the study meant that SDMT and Stroop were not compared to each other, so the order in which they were presented was not regarded as necessary to control. Rather the comparison was between the SMDT with and without distractors and separately, between the Stroop with and without distractors. Participants were assigned a medical code and odd numbered participants were given the distracter tests first, followed by the MACFIMS, which included the SDMT (administered last in this protocol), and then the Stroop. This order was reversed in the case of even numbers, whereby the non-distractor tests were administered and then the MACFIMS, followed by the distractor tests. Healthy controls and MS participants

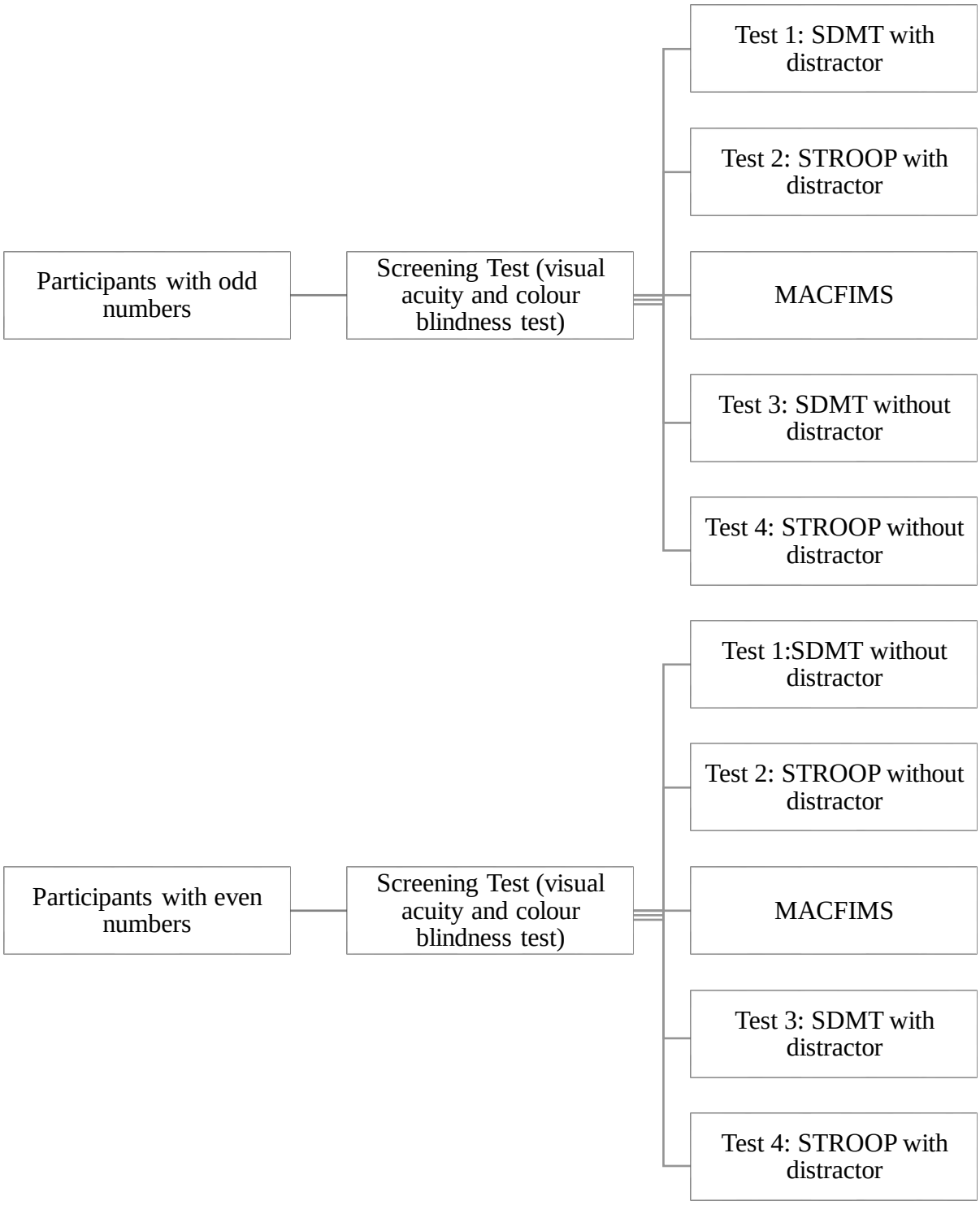


Figure 5.4

Counterbalance Design Diagram

underwent the same procedure. Testing concluded with the Hospital Anxiety and Depression Scale.

Figure 5.4 is a representation of the counterbalance design whereby the two groups of participants were divided by odd and even numbers.

Ethical considerations

Ethics approval was received through the Research Ethics Board of the hospital where the research was undertaken (Project Identification No. 140-2010; Appendix H), as well as the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (Protocol No. M170502; Appendix G). Participants were fully informed about the study and written informed consent was obtained (Appendix B.) They were told that their consent was voluntary and could leave the research at any time without prejudice. Participants were selected based on both the inclusion and exclusion criteria. In an effort to maintain confidentiality and anonymity, participants were assigned a number attached to their raw data. All test results remain in the care of the researchers and only those directly involved in the study had access to the data and personal identifying information. Upon request, participants could obtain feedback concerning their test results. Travel costs were reimbursed so that participants did not have to fund their attendance. Since the time for the testing was fairly lengthy, up to three hours, there were appropriate breaks between tests. The tests were non-invasive and participants did not complain about any adverse effects during or following the assessment process.

Data analysis

Exploratory Data Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS), IBM SPSS ® 26 Package. All psychometric data (demographic and cognitive tests) were assessed to determine whether they conformed to a Gaussian (normal) distribution. This was done using a Shapiro-Wilk test as well as graphically. If the distribution was normal then appropriate analytical tools were employed to fit the distribution of the data such as Mann-Whitney U tests and Poisson regression Norman & Shreiner, 2003).

Demographic and MS Disease-Related Variables

Cognitive data are influenced by demographics (age, gender and years of education), disease related variables (EDSS score and disease duration) and mental state (Amato, Zipoli et al., 2006; Kalb et al., 2018; Schultz et al., 2006). Therefore, it was important to compare groups (RRMS versus healthy controls, intact RRMS versus impaired RRMS and healthy controls versus intact RRMS) on these covariates using independent-sample t-tests for continuous normally distributed data. The Mann-Whitney U tests were utilized for continuous non-normally distributed data and chi-square tests for categorical variables, or Fisher's exact tests in the case of low expected cell sizes, specifically a cell count lower than 5.

MACFIMS tests, SDMT with Distractors and Stroop, with and without Distractors

The SDMT with distractors and the Stroop with and without distractors were included as three additional tests together with the 11 MACFIMS subtests in this study. Bivariate correlations between pairs of the 11 MACFIMS indices and the three additional tests were also analyzed using Pearson Correlation Coefficients to determine whether they were related or tapped into similar constructs. Given that the SDMT and the Stroop processing speeds decrease

with cognitive impairment, it was expected that the correlation coefficient between these two tests, computed separately, and the other 10 indices would be negative.

Defining Cognitively Intact and Impaired Groups

Participants with RRMS were compared to healthy controls. According to the performance on the MACFIMS, the MS group was divided into two subgroups, namely cognitively intact and impaired. Failure on three or more of the 11 MACFIMS indices indicated impairment. Scores of 1.5 standard deviations or more below the mean scores of the healthy control group determined failure on an individual test. There was one exception to this, which was the computerized SDMT. If time taken on this test was 1.5 standard deviations or more above that of the control group, this result was deemed a failure, as this is indicative of a longer processing speed. Taking into consideration that the SDMT was performing two roles, one as part of the MACFIMS and secondly, as central to the research hypothesis, the MACFIMS data were analyzed both with and without the SDMT to detect global impairment. Therefore, global impairment was looked at two way; first, with failure on three or more out of 11 tests falling 1.5 SD or more below the mean of the healthy control group (Criterion 1; SDMT 1.5 SD or more above the mean), and second, a failure of three or more out of 10 indices excluding performance on the SDMT (Criterion 2). These two comparisons were used to evaluate any possible confounding of the dual role of the SDMT.

The SDMT and the Stroop provided two types of data, namely the time to complete the test (measured in seconds) and the errors made in doing so. Previous research with these tests has shown time to completion to be the more important of the two, given that error rates are generally very low. In a comparison of people with MS and healthy controls, errors made by both groups averaged fewer than one error per trial and therefore, processing time rather than

error rate was considered (Hughes et al., 2013). However, for the purpose of this study both processing speed and number of errors were recorded and constituted dependent variables. The error rates on both the SDMT and Stroop were so low, that the analyses of errors was subsidiary. Based on the argument given earlier, it was anticipated and hypothesized that the time taken to complete the tests would produce the most meaningful results. To summarize, this study examined the participants' performance on fourteen subtests and the number of errors made on four tests, namely, SDMT with and without distractors and Stroop with and without distractors. Impairment rates on each of the 11 MACFIMS indices and global impairment rates between healthy controls and RRMS group were compared using chi-square statistics.

Sensitivity Tests

Sensitivity and specificity calculations were conducted for each of 11 MACFIMS indices in detecting global cognitive impairment relative to the MACFIMS using the two sets of standards (including and excluding performance on the SDMT). This was carried out in order to determine if there were practice effects as a result of the close repetition of the tests with and without distractors. Sensitivity refers to a test's ability to discriminate the percentage of individuals who have a positive score on a test compared to a 'gold standard test', in this case the MACFIMS. Conversely specificity refers to the ability of a test to detect a negative score designated as a percentage on a test compared to the gold standard. On the 11 MACFIMS subtests, failure on three or more cognitive indices served as the standard for global cognitive impairment. This study additionally used a different standard of failing three or more of the MACFIMS tests (10 subtests) excluding the SDMT due to possible practice effects.

Receiver operating characteristic (ROC) analyses were also undertaken to evaluate the discriminative value of each test, namely, how well the test could discriminate between

impaired and intact cognition for all study participants. Therefore, sensitivity on the SDMT and the Stroop both with distractors would be obtained if failure of 1.5 SD and above that of healthy control was detected. These scores were then compared to failure of three subtests or more on the MACFIMS to calculated sensitivity percentages. This was inversely the case with specificity. If no failure (a pass) was detected in the SDMT and the Stroop with distractors, this was compared with a pass, or being cognitively intact on the MACFIMS.

Inferential Analyses

Two set of exploratory analyses were run to compare the three groups (healthy controls, RRMS intact and RRMS impaired) for possible differences in the processing speed of SDMT and the Stroop under two conditions, without and with distractors.

To compare this serial data between the three groups a two-factor repeated-measures analysis of covariance (RANCOVA) was utilized to test within and between subject influences on the SDMT and the Stroop processing speeds over two tasks, non-distractors and distractors. The model contained a group (healthy controls and total RRMS), task (with and without distractors), and a group by task interaction term. Within each task, comparisons were undertaken across the three groups. Within each group, comparisons were also made between type of task (distractors and non-distractors). The key variable in the two-factor repeated measures RANCOVA model was the interaction between task and group. This tested whether there were differences in outcome between the two tasks across the three groups. If the interaction term was found to be statistically significant, then post hoc analyses were carried out to establish the specific group and task differences that were behind the statistical significance.

The purpose of including covariates in the analyses was to partial-out their potential effects on the dependent variables. The covariates included study design (counterbalance), demographic information (age, years of education, gender and employment status), mental health (HADS anxiety and depression scores) and cognitive (WTAR Score) variables. Post-hoc Tukey analyses were undertaken to determine between group variance for the three groups. A similar repeated-measures of RANCOVA model including the same eight covariates was used to assess the Stroop processing speed between the three groups over the two tasks, non-distractor versus distractor.

The number of errors measured on the SDMT was low and not normally distributed. To determine which variables could predict errors a Poisson regression analysis was undertaken. The Poisson regression model using the count of errors as a dependent variable and the same eight variables in the previous model as covariates was conducted to assess differences between groups (healthy controls, RRMS intact and RRMS impaired) and across task (without and with distractor). A similar Poisson regression model was conducted using the count of errors made on Stroop as the dependent variable and the same set of covariates. A summary of the purpose of analysis and associated statistic used is provided in Table 3.

Conclusion

This chapter presented the research methodology used in this study. The first section outlined the research design and central research questions, namely whether auditory distraction negatively impacts processing speed in cognitively intact people with RRMS compared to healthy controls. Unintelligible speech distractors were embedded in the SDMT and the Stroop in order to test this hypothesis and performance was compared on these tests

with and without distractors. An overview of the data analyses was provided and detailed results of the statistical analyses follows in the next chapter.

Table 5.3

Purpose of each analysis and statistical method employed

Purpose	Statistical Methods
1. Determined data distribution	Skewness, Kurtosis and Shapiro-Wilk Test of Normality as well as Histograms
2. Between group comparisons on demographic variables	Independent sample t-tests were used to compare normally distributed ordinal data and a Mann-Whitney U test for non-normally distributed ordinal data. Categorical data were compared using chi-squared (χ^2) analyses
3. Inter-relationship between test pairs (11 MACFIMS indices, the Stroop with and without distractors and the SDMT with distractors)	Pearson Product-Moment Correlation Analyses and Spearman if not normally distributed
4. Discriminating power of each of MACFIMS indices on global impairment	Receiver-operating-characteristic (ROC) curve analysis
5. Evaluation of practice effects	Sensitivity Test
6. Within and between group comparisons for each group (healthy controls, intact RRMS and impaired RRMS) on the SDMT with and without distractors	Two-factor repeated-measures RANCOVA using the SDMT processing speed as the dependent variable and follow-up post-hoc analysis
7. Within and between group comparisons for each group (healthy controls, intact RRMS and impaired RRMS) on the Stroop with and without distractors	Two-factor repeated measures RANCOVA using the Stroop processing speed as the dependent variable and follow-up post-hoc analysis
8 Between group (healthy control, intact RRMS and impaired RRMS) comparisons on number of errors on the SDMT under each condition (no distractors and with distractors) while controlling for the effect of other continuous variables which co-vary with the dependent variable	Poisson Regression using the number of errors made on the SDMT as dependent variable
9. Between group (healthy control, intact RRMS and impaired RRMS) comparisons on number of errors made on the Stroop under each condition (no distractors and with distractors) while controlling for the effect of other continuous variables which co-vary with the dependent variable	Poisson Regression using the number of errors made on the Stroop as dependent variable

CHAPTER 6

RESULTS

Introduction

This chapter encompasses the results of the descriptive and inferential analyses carried out to answer the research question, '*Does auditory distraction impact information processing speed in people with RRMS who test as cognitively intact on the MACFIMS compared to healthy controls?'* The aim of the study was to investigate the impact of auditory distraction on processing speed in people with RRMS. This was implemented by embedding unintelligible speech as a source of distraction into two neuropsychological tests that tap into processing speed, namely, the SDMT and the Stroop. The healthy control group met the same inclusion and exclusion criteria as the RRMS group and was matched to this group on demographic measures. Clearly matching did not occur on the MS related variables, the EDSS scores and disease duration. The RRMS group was then divided into intact and impaired according to pass or failure on the MACFIMS. Within group analyses were conducted on these groups to assess for differences in performance on the SDMT (with and without distractors) and the Stroop (with and without distractors). Between group analyses were performed between the cognitively intact RRMS group and healthy controls. The cognitively intact group was chosen as the focus of comparison with the control group as it was hypothesized that subtle cognitive impairment is often not revealed in commonly used cognitive batteries in this group. The analyses were conducted using the IBM SPSS ® 26 Package.

Summary of Statistical Analyses

The following analyses were implemented. Initially demographic (age, gender, years of education, WTAR), multiple sclerosis (disease duration, EDSS) and mental health (HADS) data were presented, as cognitive data could be influenced by these covariates. The data was assessed for normality using Shapiro-Wilk normality tests and histograms. The same statistical methodology was then applied to the cognitive tests, namely the MACFIMS, the SDMT (with distractors) and the Stroop (with and without distractors), totaling 14 subtests, to test for normality. Pearson bivariate correlations coefficients were obtained for the 14 subtests to determine the relationship between the various cognitive measures. A comparison between the healthy control and RRMS groups on the demographic variables was computed, followed by a comparison between these groups on the cognitive tests. Global impairment was calculated according to scores on the MACFIMS. Based on impairment rates the RRMS group was subdivided into cognitively impaired and cognitively intact groups. Receiver-operating-characteristic (ROC) curve analyses were calculated to illustrate how well each of the MACFIMS tests, the Stroop (with and without distractors) and the SDMT (with distractors) were able to discriminate between participants who were cognitively impaired or intact. Demographic and neuropsychological test data were then compared between the cognitively intact and impaired RRMS groups. Since the SDMT (without distractors) was part of the MACFIMS and was also a dependent variable with distractors, possible confounding effects could influence the results. As such, instead of taking global impairment as a failure of three or more on the 11 MACFIMS tests, impairment was determined as failure on three out of 10 MACFIMS tests with the SDMT removed. Sensitivity and specificity for the 14 subtests were obtained for global impairment and the total numbers in the impaired and intact RRMS groups

were then revised based on the second version of three failures out of 10 on the MACFIMS. Two-way repeated measures analyses of covariance (RANCOVA) were conducted between the three research groups to reveal whether or not changes in processing speed on both the SDMT (with and without distractors) and the Stroop (with and without distractors) were the result of an interaction between the groups. The RANCOVA was suitable because of the close matching of the groups on demographic variables. Poisson regression analyses were conducted on errors made by the three groups on the SDMT (with and without distractors) and the Stroop (with and without distractors) to establish whether there was any significant variance between the groups on error scores. In order to answer the primary research question, group comparisons between the healthy controls and cognitively intact RRMS groups were undertaken on demographic characteristics, test results on the MACFIMS, and processing speed and errors on the SDMT (with and without distractors) and the Stroop (with and without distractors), using the revised numbers obtained from the sensitivity calculations. In order to cross-check whether the SDMT was potentially a confounder, a comparison was completed between the healthy control and the cognitively intact RRMS groups with the SDMT included in the MACFIMS. This confirmed the numbers obtained by the sensitivity and specificity tests in the second version of the MACFIMS, namely three out of 10 indices. A detailed discussion of each of these analyses is provided below.

Demographic and Multiple Sclerosis Related Data

A total of 80 RRMS and 50 healthy control participants were recruited. One RRMS subject was removed from the analyses due to incomplete test data. Therefore, the final sample for analysis included 79 RRMS and 50 healthy control participants, providing a total of 129. The participants' age, highest level of education, WTAR score and HADS scores (Anxiety,

Depression and Total) were recorded. The EDSS score and disease duration for RRMS participants were also recorded, with one missing value, as the treating neurologist was unable to supply this information. The initial analyses for these variables involved calculations of skewness and kurtosis, as well as Shapiro-Wilk tests of normality and histograms to assess the appropriateness of their inclusion or exclusion as covariates in the inferential models (Ghasemi & Zahediasl, 2012). A single model was run to address the relationship between the variables on the one hand and on the other, the two groups, healthy controls and RRMS (n = 129). The assumption of normality was linked to the single model, rather than the two groups separately. The supposition inherent in this approach is that if the entire sample was normally distributed then parametric statistics could be used to compare the relevant groups on all variables. Therefore, comparisons were not undertaken to evaluate if the variables contained within the two groups were normally distributed, but rather that each variable across groups was normally distributed (Kleinbaum et al., 2014). This allowed for an assessment of the relationship across the groups on demographic, mental health, cognitive (Table 6.1, p. 213) and assessment data (Table 6.2, p. 214)

Normality of Distribution of Cognitive and Mental Health Variables

When the values of skewness, a measure of the symmetry in a distribution, and kurtosis, the degree of peakedness of a distribution, are in the range between 1.00 and -1.00, the presentation of the data is generally considered as being close to a normal distribution (Rosenthal & Rosnow, 2008). The Shapiro-Wilk normality tests revealed that all variables in Table 6.1 (p. 213), with the exception of the WTAR score, were found to be statistically non-normal. However, as mentioned previously, histograms were created for each variable. The plots that would be of concern were those that were highly skewed (i.e. a long tail for the

distribution to the right or left), or those that were bimodal (two clear peaks that are fairly far apart on the plot). Any plots that were approximately normal, along with the Central Limit Theorem, would allow the use of parametric testing in this study. The Central Limit Theorem states that as the sample size increases, the mean of a variable becomes closer to a normal distribution (Salkind, 2012). The sample size considered large enough for the Central Limit Theorem to hold is a sample of 30 and this study worked with a sample larger than that. For the Shapiro-Wilk test, the null hypothesis requires normal distribution therefore, a significant *p*-value leads to the rejection of normality. However, tests of normality are sensitive to minor deviations from normality, therefore this study also used histograms and the Central Limit Theorem to make decisions regarding variables.

Figure 6.1 (Figures 6.1 to 6.8 can be viewed in Appendix I) represents the histogram for the age of the participants in the study. Table 6.1 (p. 213) shows the variance in age ranging from a minimum of 20 years to a maximum of 60 years. The values of dispersion in the age range (*var* = 92.674, *SD* = 9.627, *SE* = 0.848) indicated large variability of the data whilst the values for skewness and kurtosis were an acceptable -0.076 (*SE* = 0.213) and -0.918 (*SE* = 0.423) respectively. The Shapiro-Wilk test of normality for age indicated that it was not normally distributed based on the significant test result (*S-W* = 0.973, *p* = .011). Participants' age had a peak between 30 and 50, as a larger proportion of the sample recruited in this study were either young or middle-aged adults. While the Shapiro-Wilk statistic indicated non-normality, the histogram is approximately normal and this along with the Central Limit Theorem supported the use of parametric tests.

The years of education variable ranged from a minimum of 10 years to a maximum of

20 years. It had dispersion with variance of 3.642 (*SD* = 1.909, SE = 0.168) and an acceptable skewness value of -0.152 (*SE* = 0.213) and kurtosis value of 0.169 (*SE* = 0.423). The Shapiro-Wilk test of normality for education indicated that it was not normally distributed based on the significant test result (*S-W* = 0.934, *p* < .001). Figure 6.2 (p. 215) represents the histogram for the education of the participants in the study. The peak of the distribution was 16 years, which indicated that the majority of the participants in this sample received a tertiary education. While the Shapiro-Wilk statistic indicated non-normality, the histogram is approximately normal and supported the use of parametric tests.

The WTAR score ranged from a minimum of 20 to a maximum of 49. The dispersion indicated a fairly high variance of 30.296 (*SD* = 5.504, *SE* = 0.498). It had an acceptable skewness value of -0.207 (*SE* = 0.219) and kurtosis value of 0.217 (*SE* = 0.435). The Shapiro-Wilk test of normality for WTAR indicated that it was normally distributed based on the non-significant test result (*S-W* = 0.987, *p* = .290). Figure 6.3 represents the histogram for the WTAR scores of the participants in the study. While the Shapiro-Wilk statistic indicated a normal distribution and the histogram is bell shaped as well, thus parametric tests were used.

The HADS subscale score for anxiety ranged from a minimum value of 0 to a maximum value of 20. The dispersion had a variance of 22.490 (*SD* = 4.742, *SE* = 0.418). It had an acceptable skewness value of 0.287 (*SE* = 0.213) and kurtosis value of -0.756 (*SE* = 0.423). The Shapiro Wilk test of normality for HADS anxiety indicated that it was not normally distributed based on the significant test result (*W-S* = 0.968, *p* = .004). The histogram for the HADS anxiety subscale scores of the participants in the study can be viewed in Figure 6.4. While the Shapiro-Wilk statistic indicated non-normality, the histogram is approximately normal and supported the use of parametric tests.

The HADS subscale score for depression ranged from a minimum value of 0 to a maximum value of 17. The dispersion had a variance of 16.174 (*SD* = 4.022, *SE* = 0.354). It had an acceptable skewness value of 0.52 (*SE* = 0.213) and kurtosis value of -0.592 (*SE* = 0.423). The Shapiro-Wilk test of normality for HADS depression indicated that it was not normally distributed based on the significant test result (*S-W* = 0.942, $p < .001$). Figure 6.5 represents the histogram for the HADS depression subscale scores of the participants in the study. While the Shapiro-Wilk statistic indicated non-normality, the histogram is approximately normal and this supported the use of parametric tests.

The HADS total score ranged from a minimum value of 0 to a maximum value of 34. The dispersion had a variance of 65.519 (*SD* = 8.094, SE = 0.713). It had an acceptable skewness value of 0.29 (*SE* = 0.213) and kurtosis value of -0.776 (*SE* = 0.423). The Shapiro Wilk test of normality for HADS total score indicated that it was not normally distributed based on the significant test result (*W-S* = 0.971, $p = .007$). The histogram for the HADS total scores of the participants in the study is represented in Figure 6.6. While the Shapiro-Wilk statistic indicated non-normality, the histogram is approximately normal and this supported the use of parametric tests.

EDSS score for RRMS participants ranged from a minimum value of 0 to a maximum value of 7. It is worth noting that the EDSS mean score for all RRMS participants was 2.04, indicating a mild physical disability. There was one participant with an EDSS score of 7 who was still assessed as relapsing remitting by the attending neurologist, but was considered an outlier adnd did nto influence the use of paramentric statistics. The dispersion had a variance of 2.053 (*SD* = 1.433, *SE* = 0.162). It had a skewness value of 1.657 (*SE* = 0.272) and kurtosis value of 2.829 (*SE* = 0.538), which were outside of the target range of -1 to +1. The Shapiro-

Wilk test of normality for EDSS indicated that it was not normally distributed based on the significant test result (*S-W* = 0.818, $p < .001$). Figure 6.7 depicts the histogram for the EDSS scores of the participants in the study. The variable does have a slight skew to the right while the Shapiro-Wilk statistic indicated non-normality, the histogram is approximately normal and supported the use of parametric tests.

Disease duration for RRMS subjects ranged from a minimum value of 2.49 years to 32.49 years. It had dispersion with variance of 54.003 (*SD* = 7.349, *SE* = 0.843) and an acceptable skewness value of 0.744(*SE* = 0.276) and kurtosis value of 0.008 (*SE* = 0.545). The Shapiro-Wilk test of normality for disease duration indicated that it was not normally distributed based on the significant test result (*S-W* = 0.936, $p = .001$). Figure 6.8 represents the histogram for the years of duration of the disease in the participants in the study. The variable does have a skew to the right. While the Shapiro-Wilk indicated non-normality, the histogram is approximately normal and supported the use of parametric tests.

Table 6.1 on page 213 shows the distribution characteristics of the demographic, cognitive and mental health variables.

Normality of distribution of the MACFIMS, SDMT with distractors and Stroop, with and without distractors

The participants' scores on 11 MACFIMS subtests, the SDMT (with distractors) and the Stroop (with and without distractors) were examined individually. The descriptive statistics and distributions are presented in Table 6.2 (p. 214) and Figures 6.9 to 6.26. The figures can be view in Appendix J. As indicated by the 14 histograms, no outliers were identified as likely to affect the distribution of the scores in any of the 14 subtests. All test were examined in terms of histograms and used the conceptualization of the Central Limit Theorem.

The PASAT - 3 second score ranged from a minimum value of 12 to a maximum value of 60. It had an acceptable skewness value of -0.754 (*SE* = 0.219) and kurtosis value of -0.167 (*SE* = 0.435). The Shapiro-Wilk test of normality for the PASAT-3 seconds indicated that in was not normally distributed based on the significant test result (*S-W* = 0.959, *p* = .003). Figure 6.9 represents the histogram for the PASAT - 3 second score of the participants in the study. The histogram has a slight skew to the left, but is approximately normal and supported the use of parametric tests. The PASAT-2 second score ranged from a minimum value of 17 to a maximum value of 56. It had an acceptable skewness value of -0.496 (*SE* = 0.465). The Shapiro-Wilk test of normality for PASAT-2 seconds indicated that it was normally distributed based on the non-significant test result (*S-W* = 0.986, *p* = .348). Figure 6.10 depicts the histogram for the PASAT 2-second score of the participants in the study and supported the use of parametric tests.

The CVLT-II total recall score ranged from a minimum value of 23 to a maximum value of 72. It had an acceptable skewness value of -0.394 (*SE* = 0.213) and kurtosis value of -0.542 (*SE* = 0.423). The Shapiro-Wilk test of normality for the CVLT-II total recall indicated that it was not normally distributed based on the significant test result (*S-W* = 0.972, *p* = .028). Figure 6.11 presents the histogram for the CVLTII total score of the participants in the study. While the Shapiro-Wilk statistic indicated non-normality, the histogram is approximately normal and supported the use of parametric tests.

The CVLT-II delayed recall score ranged from a minimum value of 2 to a maximum value of 16. It had an acceptable skewness value of -0.605 (*SE* = 0.213) and kurtosis value of -0.48 (*SE* = 0.423). The Shapiro-Wilk test of normality for the CVLT-11 total recall indicated that it was not normally distributed based on the significant test result (*S-W* = 0.945,

$p <$ .001).The histogram for the CVLT-II delayed recall score of the participants in the study can be seen in Figure 6-12. While the Shapiro-Wilk statistic indicated non-normality, the histogram has a slight skew to the left, but is approximately normal and supported the use of parametric tests.

The BVMT-R total recall score ranged from a minimum value of 8 to a maximum value of 36. It had an acceptable skewness value of -0.03 (*SE* = 0.214) and kurtosis value of -0.896 (SE = 0.425). The Shapiro-Wilk test of normality for the BVMT-R total recall score indicated that it was normally distributed based on the non-significant test result (*S-W* = 0.981, *p* = .151). Figure 6.13 signifies the histogram for the BVMT-R total recall score of the participants in the study. The Shapiro-Wilk statistic indicated normality supported by the histogram.

The BVMT-R delayed recall score ranged from a minimum value of 0 to a maximum value of 12. It had an acceptable skewness value of -0.856 (*SE* = 0.214) and kurtosis value of -0.155 (*SE* = 0.425). The Shapiro-Wilk test of normality for the BVMT-R delayed recall score indicated that it was not normally distributed based on the significant test result (*S-W* = 0.908, $p <$ .001). Figure 6.14 represents the histogram for the BVMT-R delayed recall score of the subjects in the study and while the histogram has a slight skew to the left it is approximately normal and thus supported the use of parametric tests.

The D-KEFS sorting score ranged from a minimum value of 3 to a maximum value of 15. It had an acceptable skewness value of -0.16 (*SE* = 0.213) and kurtosis value of -0.293 (*SE* = 0.423). The Shapiro-Wilk test of normality for the D-KEFS sorting score indicated that it was not normally distributed based on the significant test result (*S-W* = 0.975, *p* = .046). The histogram for the D-KEFS sorting score revealed in Figure 6.15 is approximately normal and supported the use of parametric tests.

The D-KEFS description score ranged from a minimum value of 8 to a maximum value of 56. It had an acceptable skewness value of 0.195 (*SE* = 0.213) and kurtosis value of -0.087 (S*E* = 0.423). The Shapiro Wilk test of normality for the D-KEFS sorting score indicated that it was normally distributed based on the non-significant test result (*S-W* = 0.985, *p* = .314) and this was supported by the histogram seen in Figure 6-16.

The COWAT score ranged from a minimum value of 14 to a maximum value of 92. It had a skewness value of 1.152 (*SE* = 0.215) and kurtosis value of 2.702 (*SE* = 0.427) which were outside of the target range of -1 to +1. The Shapiro-Wilk test of normality for the COWAT score indicated that it was not normally distributed based on the significant test result (*S-W* = 0.920, *p* < .001). Figure 6.17 represents the histogram for the COWAT score of the participants in the study. While the Shapiro-Wilk statistic indicated non-normality, the histogram has a slight skew to the right, but is approximately normal and this supported the use of parametric tests.

The JLO score ranged from a minimum value of 3 to a maximum value of 30. It had a skewness value of -0.996 (*SE* = 0.213) and kurtosis value of 1.012 (*SE* = 0.423). The kurtosis values were slightly outside of the target range of -1 to +1. The Shapiro-Wilk test of normality for the JLO score indicated that it was not normally distributed based on the significant test result (*S-W* = 0.925, *p* < .001). Figure 6.18 denotes the histogram for the JLO score of the participants in the study. While the Shapiro-Wilk statistic indicated non-normality, the histogram has a slight skew to the left, but is approximately normal and so supported the use of parametric tests.

The SDMT (without distractors) score ranged from a minimum value of 9.550 to a maximum value of 27.640. It had a skewness value of 1.597 (*SE* = 0.213) and kurtosis value

of 3.222 (*SE* = 0.423) which were outside of the target range of -1 to +1. The Shapiro-Wilk test of normality for the SDMT (without distractors) score indicated that it was not normally distributed based on the significant test result (*S-W* = 0.888, $p < .001$). The histogram for this test (Figure 6-19) has a slight skew to the right but is approximately normal and this supported the use of parametric tests. The SDMT (with distractors) score ranged from a minimum value of 9.660 to a maximum value of 30.600. It had a skewness value of 1.643 (*SE* = 0.213) and kurtosis value of 2.881 (*SE* = 0.423) which were outside of the target range of -1 to +1. The Shapiro-Wilk test of normality for the SDMT (with distractors) score indicated that it was not normally distributed based on the significant test result (*S-W* = 0.883, $p < .001$). However, the histogram presented in Figure 6.20 has a slight skew to the right but is approximately normal and supported the use of parametric tests.

The Stroop (without distractors) score ranged from a minimum value of 13.720 to a maximum value of 67.080. It had a skewness value of 1.545 (*SE* = 0.213) and kurtosis value of 4.151 (*SE* = 0.423) which were outside of the target range of -1 to +1. The Shapiro-Wilk test of normality for the Stroop (without distractors) score indicated that it was not normally distributed based on the significant test result (*S-W* = 0.850, $p < .001$). Figure 6-21 represents the histogram for the Stroop (without distractors) score of the participants in the study. The histogram has a slight skew to the right but is approximately normal and thus, supported the use of parametric tests. The Stroop (with distractors) score ranged from a minimum value of 13.600 to a maximum value of 70.250. It had a skewness value of 1.709 (*SE* = 0.213) and kurtosis value of 4.014 (*SE* = 0.423) which were outside of the target range of -1 to +1. The Shapiro-Wilk test of normality for the Stroop (with distractors) score indicated that it was not normally distributed based on the significant test result (*S-W* = 0.853, $p < .001$). The histogram

for this test (Figure 6.22) has a slight skew to the right but is approximately normal and supported the use of parametric tests.

The number of errors for the SDMT (without distractors) ranged from a minimum value of 0 to a maximum value of 6. It had a skewness value of 2.188 (*SE* = 0.214) and kurtosis value of 5.622 (*SE* = 0.425) which were outside of the target range of -1 to +1. The Shapiro-Wilk test of normality for the SDMT (without distractors) score indicated that it was not normally distributed based on the significant test result (*S-W* = 0.676, $p < .001$). Figure 6.23 represents the histogram on this test and is clearly skewed to the right. Therefore, this variable was analyzed using non-parametric statistics. The number of errors for the SDMT (with distractors) ranged from a minimum value of 0 to a maximum value of 5. It had a skewness value of 1.725 (*SE* = 0.214) and kurtosis value of 2.559 (*SE* = 0.425) which were outside of the target range of -1 to +1. The Shapiro-Wilk test of normality for the SDMT (with distractors) score indicated that it was not normally distributed based on the significant test result (S-W = 1.682, $p < .001$). The histogram for this test (Figure 6.24) indicated non-normality as it is clearly skewed to the right. Thus, this variable was analyzed using non-parametric statistics.

The number of errors for the Stroop (without distractors) ranged from a minimum value of 0 to a maximum value of 9. It had a skewness value of 3.979 (*SE* = 0.214) and kurtosis value of 18.333 (*SE* = 0.425) which were outside of the target range of -1 to +1. The Shapiro-Wilk test of normality for the Stroop (without distractors) score indicated that it was not normally distributed based on the significant test result (*S-W* = 0.397, $p < .001$). The histogram in Figure 6.25 revealed non-normality, and is clearly right skewed and so this variable was analyzed using non-parametric statistics. The number of errors for the Stroop (with distractors) ranged from a minimum value of 0 to a maximum value of 7. It had a skewness value of 3.796

(*SE* = 0.214) and kurtosis value of 16.013 (*SE* = 0.425) which were outside of the target range of -1 to +1. The Shapiro-Wilk test of normality for the Stroop (with distractors) score indicated that it was not normally distributed based on the significant test result (test statistic = 0.410, $p < .001$). In Figure 6.26 the histogram is clearly right skewed and non-parametric statistics were used.

Examination of the 14 cognitive tests revealed that five of the 14 were found to have skewness and kurtosis values outside of the target range of -1 to +1. They were the COWAT, the SDMT (without distractors), the SDMT (with distractors), the Stroop (without distractors) and the Stroop (with distractors). For the 14 cognitive tests, three were found to be normally distributed based on the Shapiro-Wilk test. They were the PASAT-2 seconds), the BVMT-R total recall, and the D-KEFS description scale.

As mentioned previously, tests of normality are sensitive to minor deviations from normality, therefore, this study also utilized histograms and the Central Limit Theorem to make decisions regarding variables. The tests of normality for the MACFIMS and the additional tests can be seen in Table 6.2 (p. 214). All tests except the PASAT – 2 second, BVMT-R – total recall and D-KEFS – Sorting were statistically significant indicating the use of non-parametric statistics. However, examination of the histograms revealed normal curves with little skewing. This held true except for the four error scores for the SDMT (with and without distractors) and the Stroop (with and without distractors), which were treated with non-parametric statistics.

The descriptive statistics and distributions are presented for the cognitive tests in detail in Table 6.3 (p. 215), including mean, range standard error (*SE*), standard deviation (*SD*), skewness and kurtosis.

Table 6.1

Descriptive statistics and tests of normality of demographic, cognitive and mental health variables

		Range			Dispersion			Normality				Test of normality	
	N	Min	M	Max	Var	SD	SE	Skewness	$SE_{Skewness}$	Kurtosis	$SE_{Kurtosis}$	Shapiro-Wilk	*p*
Age (Years)	129	20	42.326	60	92.674	9.627	0.848	-0.076	0.213	-0.918	0.423	0.973	.011*
Education (Years)	129	10	15.512	20	3.642	1.909	0.168	-0.152	0.213	0.169	0.423	0.934	<.001***
WTAR score	122	20	36.697	49	30.296	5.504	0.498	-0.207	0.219	0.217	0.435	0.987	.290
HADS score													
Anxiety	129	0	7.868	20	22.490	4.742	0.418	0.287	0.213	-0.756	0.423	0.968	.004**
Depression	129	0	5.512	17	16.174	4.022	0.354	0.52	0.213	-0.592	0.423	0.942	<.001***
Total	129	0	13.380	34	65.519	8.094	0.713	0.29	0.213	-0.776	0.423	0.971	.007**
EDSS Score	78	0	2.045	7	2.053	1.433	0.162	1.657	0.272	2.829	0.538	0.818	<.001***
Disease Duration (Years)	76	2.49	12.125	32.49	54.003	7.349	0.843	0.744	0.276	0.008	0.545	0.936	.001**

*p = .05
** p < .01
*** p < .001
Key: WTAR – Wechsler Test of Adult Reading; HADS – Hospital Anxiety and Depression Scale; EDSS – Expanded Disability Status Scale

Table 6.2

Tests of Normality of MACFIMS 11 subtests, SDMT with Distractors, Stroop with and without Distractors

	Test of normality	
	Shapiro-Wilk	p
MACFIMS		
PASAT – 3 second	0.959	.003**
PASAT – 2 second	0.986	.348
CVLT-II - Total	0.972	.028*
CVLT-II – short delay	0.945	<.001***
CVLT-II – long delay	0.927	<.001***
BVMT-R – total recall	0.981	.151
BVMT-R – delayed recall	0.908	<.001***
D-KEFS – Sorting	0.975	.046*
D-KEFS – Description	0.985	.314
COWAT	0.920	<.001***
JLO	0.925	<.001***
SDMT no distractor	0.888	<.001***
Other Cognitive Tests		
SDMT with distractors	0.883	<.001***
Stroop without distractors	0.850	<.001***
Stroop with distractors	0.853	<.001***
No. of Errors		
SDMT without distractors	0.676	<.001***
SDMT with distractors	1.682	<.001***
Stroop without distractors	0.397	<.001***
Stroop with distractors	0.410	<.001***

*$p < .05$ ** $p < .01$ *** $p < .001$

Key; PASAT – 3: Paced Auditory Serial Addition Test – 3 second; PASAT – 2: Paced Auditory Serial Addition Test – 2 second; CVLT-11: California Verbal Learning Test; BVMT: Brief Visual Learning Test-Revised; D-KEFS: Delis-Kaplan Executive Function System; COWAT: Controlled Oral Word Association Test; JLO: Judgment of Line Orientation; SDMT: Symbol Digit Modalities Test

Table 6.3

Descriptive Statistics and Normality Statistics of MACFIMS 11 subtests, SDMT with Distractors and Stroop with and without Distractors

		Descriptive Statistics					Skewness		Kurtosis		Test of normality	
	N	Max	Min	M	SE	SD	Statistics	SE	Statistics	SE	Shapiro-Wilk	p
MACFIMS												
PASAT – 3 seconds	122	60	12	43.959	1.045	11.544	-0.754	0.219	-0.167	0.435	0.959	.003**
PASAT – 2 seconds	106	56	17	34.877	0.853	8.778	0.071	0.235	-0.496	0.465	0.986	.348
CVLT-II- total recall	129	72	23	50.798	1.018	11.557	-0.394	0.213	-0.542	0.423	0.972	.028*
CVLT-II – delayed recall	129	16	2	10.899	0.325	3.691	-0.605	0.213	-0.48	0.423	0.927	<.001***
BVMT-R – total recall	128	36	8	20.898	0.629	7.120	-0.03	0.214	-0.896	0.425	0.981	.151
BVMT-R – delayed recall	128	12	0	8.281	0.254	2.870	-0.856	0.214	0.155	0.425	0.908	<.001***
D-KEFS – Sorting	129	15	3	8.907	0.222	2.523	-0.16	0.213	-0.293	0.423	0.975	.046*
D-KEFS – Description	129	56	8	31.543	0.827	9.396	0.195	0.213	-0.087	0.423	0.985	.314
COWAT	127	92	14	39.630	1.156	13.029	1.156	0.215	2.702	0.427	0.920	<.001***
JLO	129	30	3	22.907	0.453	5.148	-0.996	0.213	1.012	0.423	0.925	<.001***
SDMT without distractors[1]	129	27.640	9.550	13.756	0.286	3.248	1.597	0.213	3.222	0.423	0.888	<.001***
Other Cognitive Tests[1]												
SDMT with distractors[1]	129	30.600	9.660	14.913	0.350	3.972	1.643	0.213	2.881	0.423	0.883	<.001***
Stroop without distractors[1]	129	67.080	13.720	25.479	0.747	8.479	1.545	0.213	4.151	0.423	0.850	<.001***
Stroop with distractors[1]	129	70.250	13.600	27.748	0.896	10.182	1.709	0.213	4.014	0.423	0.853	<.001***
Errors[2]												
SDMT without distractors[2]	128	6	0	0.766	0.105	1.187	2.188	0.214	5.622	0.425	0.676	<.001***
SDMT with distractors[2]	129	5	0	0.680	0.095	1.072	1.725	0.214	2.559	0.425	1.682	<.001***
Stroop without distractors[2]	129	9	0	0.461	0.119	1.345	3.979	0.214	18.333	0.425	0.397	<.001***
Stroop with distractors[2]	129	7	0	0.422	0.105	1.188	3.796	0.214	16.013	0.425	0.410	<.001***

1: response time in seconds; 2: absolute values of number of errors; M: mean: SD: standard deviation; SE: standard error;
Key; PASAT – 3: Paced Auditory Serial Addition Test – 3 second; PASAT – 2: Paced Auditory Serial Addition Test – 2 second; CVLT-11: California Verbal Learning Test; BVMT: Brief Visual Learning Test-Revised; D-KEFS: Delis-Kaplan Executive Function System; COWAT: Controlled Oral Word Association Test; JLO: Judgment of Line Orientation; SDMT: Symbol Digit Modalities Test

Table 6.4

Correlation Matrix between the MACFIMS, the SDMT with Distractors and the Stroop, with and without Distractors (n = 106-129)

		MACFIMS											Additional Tests		
		PASAT – 3 seconds	PASAT – 2 seconds	CVLT-II - Total	CVLT-II – long delay	BVMT-R – total recall	BVMT-R – delayed recall	D-KEFS – Sorting	D-KEFS – Description	COWAT	JLO	SDMT without distractors	SDMT with distractors	Stroop without distractors	Stroop with distractors
MACFIM	PASAT – 3 seconds	1													
	PASAT – 2 seconds	.763**	1												
	CVLT-II - Total	.386**	.259**	1											
	CVLT-II – delayed recall	.335**	0.163	.818**	1										
	BVMT-R – total recall	.413**	.203*	.599**	.612**	1									
	BVMT-R – delayed recall	.374**	0.172	.617**	.630**	.838**	1								
	D-KEFS – Sorting	.483**	.223*	.333**	.310**	.458**	.317**	1							
	D-KEFS – Description	.524**	.262**	.335**	.306**	.468**	.335**	.947**	1						
	COWAT	.389**	.276**	.355**	.272**	.363**	.331**	.351**	.389**	1					
	JLO	.493**	.348**	.211*	.252**	.419**	.430**	.468**	.464**	.236**	1				
	SDMT without distractors	-.465**	-.347**	-.521**	-.507**	-.460**	-.436**	-.409**	-.408**	-.393**	-.364**	1			
	SDMT with distractors	-.510**	-.375**	-.611**	-.560**	-.477**	-.491**	-.439**	-.427**	-.426**	-.383**	.860**	1		
Additional Tests	Stroop without distractors	-.475**	-.447**	-.447**	-.370**	-.360**	-.362**	-.367**	-.369**	-.474**	-.287**	.689**	.711**	1	
	Stroop with distractors	-.488**	-.455**	-.475**	-.411**	-.371**	-.358**	-.388**	-.380**	-.426**	-.265**	.621**	.721**	.917**	1

*$p < .05$
**$p < .01$
Key: PASAT – 3: Paced Auditory Serial Addition Test – 3 second; PASAT – 2: Paced Auditory Serial Addition Test – 2 second; CVLT-11: California Verbal Learning Test; BVMT: Brief Visual Learning Test-Revised; D-KEFS: Delis-Kaplan Executive Function System; COWAT: Controlled Oral Word Association Test; JLO: Judgment of Line Orientation; SDMT: Symbol Digit Modalities Test

Bivariate Correlations of MACFIMS, SDMT with Distractors and Stroop, With and Without Distractors

Pearson bivariate correlation coefficients were undertaken to evaluate the relationships between the 14 subtests scores, and thus the extent to which tests may have been tapping into similar skills. Table 6.4 (p. 216) depicts the correlation matrix between the tests. The results confirm the general structure of the instrument. Nearly all of the 91 bivariate correlations were statistically significant at the 5% or 1% level with two exceptions, namely, the PASAT – 2 seconds correlated with the CVLT-II – delayed recall, as well as the PASAT – 2 seconds correlated with the BVMT-R – delayed recall.

As anticipated, there were high positive correlations, defined as a correlation coefficient of .7 or higher, found between similar tests. Specifically, the different components of the same test tapped into similar cognitive domains, for example the PASAT (2 and 3 second), the CVLT-11 total recall and delayed, BVMT-R total recall and the DKEFS- Sorting and Description. In addition, as expected the SDMT, (with and without distractors), were highly correlated, likewise for the Stroop, (with and without distractors). Similarly, there was also a significant correlation between the SDMT (with and without distractors) and Stroop (with and without distractors) as they tap into the same core constructs.

Several moderate correlations, defined as a correlation coefficient between .4 and up to, but not including .7 were observed between the test scores. The PASAT - 3 second test had a moderate positive correlation with the BVMT-R total recall, the D-KEFS sorting, the D-KEFS description and the JLO. These tests have working memory, flexibility of thinking and problem solving in common. The CVLT-11 total test had a moderate positive correlation with the BVMT-R total recall, as well as with the BVMT-R delayed recall. The CVLT-II delayed

test had a moderate positive correlation with the BVMT-R total recall, as well as with the BVMT-R delayed recall. The significant correlations reflect the shared memory components in these tests, although they tap into this through a verbal (CLVT) and visual (BVMT) modality. The BVMT-R total recall test had a moderate positive correlation with the D-KEFS sorting, the D-KEFS description and the JLO. The BVMT-R delayed recall test had a moderate positive correlation with the JLO. By extension, both the D-KEFS sorting and descriptions subtests had a moderate positive correlation with the JLO. There are common spatial relations and classification components in these tests revealed by the positive correlations.

A number of negative correlations were shown. Moderate negative correlations, between -.4 to -.7 but not including -.7, were observed between the PASAT-3 second test, the SDMT (with and without distractors), and the Stroop (with and without distractor). Similarly, the PASAT-2 second test had a moderate negative correlation with the Stroop, (with and without distractors). These three tests are rapid serial processing (RSP) tasks and give an insight into processing speed. However, scoring differs from the PASAT (number of correct responses) and that of the SDMT and the Stroop, whereby scores are taken in time to complete the tests. Although errors are recorded these are generally few. In the case of the PASAT scores since these are taken as correct responses, a high PASAT score is cognitively advantageous, whereas a high SDMT or Stroop score indicates slower processing speed which is cognitively detrimental. Thus, it makes sense that moderate negative correlations were found between the PASAT and both the SDMT and the Stroop (Drake et al., 2010).

The CVLT-11 total test and the CVLT-11 delayed had moderate negative correlations with the SDMT (with and without distractors), the Stroop, (with and without distractors). The BVMT-R total recall, BVMT-R delayed recall tests, the DKEFS-Sorting and D-KEFS-

Description test had moderately negative correlations with the SDMT (with and without distractors). Likewise, the COWAT had a moderate negative correlation with the SDMT (with distractors) and the Stroop (with and without distractors). Once again high scores on the SDMT and Stroop indicate poor performance, slower information processing speed. Whereas a high score on the other tests reveal good performance. Good cognitive performance would therefore reveal lower scores on the SDMT and Stroop and higher scores on the other tests which would be portrayed statically as negative correlations.

The strength of correlations of tests across other domains were relatively weaker, even though some were highly statistically significant. For example, the bivariate correlation between the JLO, which assesses visuospatial orientation and the COWAT, which assesses verbal fluency, was statistically significant, but weak (r = .236, p = .008). Weak correlations indicate that there is little similarity between the different measures.

In sum, the tests that measured similar underlying constructs were significant and positively intercorrelated. It is to be expected that a well-constructed battery such as the MACFIMS will test diverse cognitive domains, and additionally that some of these functions will intersect as they may tap into some similar cognitive functions. It is interested to note that the SDMT and the Stroop were positively correlated only with each other, indicating the unique contribution they have in detecting speed of information processing which is the cognitive area predominantly impacted by MS (Hughes et al., 2013).

Demographic and Cognitive Test Comparisons Between Healthy Controls and Relapsing Remitting Multiple Sclerosis Participants

The following comparisons between healthy controls and RRMS participants showed no significant differences between the groups on age, gender, WTAR score and years of

education. Lack of significance on these variables indicated a robust matching between the two groups. Demographic comparisons between 50 healthy control and 79 RRMS participants and neuropsychological test data are displayed in Table 6.5 (p. 222). The mean age of the healthy control group was 41.46 years (*SD* = 10.20) compared to a mean age for the RRMS group of 42.87 (*SD* = 9.26), which was not statistically significant. There were 34 females in the control group representing 68% of the control sample. This compared to 55 females in the RRMS group representing 69.6% of the RRMS sample, also not a significant difference. Similarly, the mean years of education was 15.52 (*SD* = 1.31) in the control group as compared to a mean of 15.50 (*SD* = 2.21) in the RRMS group was not statistically different. In addition, WTAR scores were similar between the two groups.

The variables of employment and HAD scores revealed significant differences between the two groups. The healthy control group had 10 unemployed members which represented 20% of the sample. This was compared to 35 unemployed people in the RRMS group representing 44.3% of the sample. Due to symptoms associated with the RRMS group, a much higher proportion of the RRMS sample was unemployed as compared to the control group. This difference was statistically significant. RRMS mental health indices on the HADS anxiety and depression scales were significantly higher than the control group.

For the RRMS group, the mean duration of RRMS was 12.12 years (*SD* = 7.35), and this group had a mean EDSS score of 2.04 (*SD* = 1.43). Although the duration was lengthy the level of disability at 2 out of 10 was mild (see Appendix A for the disability scale).

Independent sample *t*-tests compared the MACFIMS cognitive data in Table 6.5 (p. 222) and revealed that the scores of the RRMS group were significantly lower than the healthy control group on the PASAT-2 and the PASAT-3 second tests, the CVLT-11 total recall and

delayed recall, the BVMT-R delayed recall, the COWAT and the SDMT (without distractors). These comparisons were all based on independent samples *t*-tests.

No statistically significant differences emerged on the independent samples *t*-tests between the RRMS and healthy control on the BVMT-R total recall, the D-KEFS sorting test, the D-KEFS description test and the JLO. The RRMS group took significantly longer time to complete the three additional tests, the SDMT (with distractors) and the Stroop (with and without distractors) compared to the healthy control group.

To summarize, statistically significant group differences were found on those neuropsychological tests that assessed information processing speed (i.e. PASAT, SDMT and Stroop), verbal and visual learning and memory (i.e. CVLT-II and BVMT-R), verbal fluency (i.e. COWAT), but not on those tests that assessed executive functioning (the D-KEFS) or visuospatial orientation (the JLO). Where significant differences were found, the RRMS group's performance was poorer than that of the healthy controls.

Global Impairment According to MACFIMS Results

Conventionally, global impairment is defined as impairment on two or more cognitive indices on the MACFIMS. In this study, impairment on an index was defined as a score falling 1.5 *SD* or more below the mean the healthy group. The frequencies and proportions of impairment on each of the 11 MACFIMS indices of the healthy group and the RRMS group are displayed in Table 6.6 (p. 23). Frequencies of impairment were highest on the SDMT and the PASAT-2 seconds, with 28.68% of all participants being classified as impaired on either of the two tests. Impairment rates of the RRMS group were significantly higher than those among the healthy controls on eight of 11 indices, excluding the D-KEFS-sorting, the

Table 6.5

Comparison between Healthy Controls and the RRMS Group Statistics on Demographic and Cognitive Tests (n = 129)

	Groups			
	Healthy Control *N* = 50	Total RRMS *N* = 79		
Demographics	Mean (*SD*)	Mean (*SD*)	*t*-test/ χ^2	*p*
Age, years	41.46(10.20)	42.87 (9.26)	-0.811	.419
Female sex — *n*(%)	34 (68.00%)	55 (69.60%)	χ^2=0.038	.846
Education, years	15.52 (1.31)	15.50 (2.21)	0.044	.965
Employment — *n*(%)				
Employed	40 (80.00%)	44 (55.70%)		
Unemployed	10 (10.00%)	35 (44.30%)	χ^2=7.962	.005**
Duration of RRMS, years	-	12.12 (7.35)		
EDSS score	-	2.04 (1.43)		
WTAR score	36.51 (5.91)	36.81 (5.26)	-0.294	.769
HADS score				
Anxiety	4.22 (3.14)	10.17 (4.09)	-9.304	<.001***
Depression	2.44 (2.43)	7.45 (3.60)	-9.448	<.001***
Total	6.66 (4.95)	17.63 (6.69)	-10.668	<.001***
MACFIMS				
PASAT – 3 seconds	46.46 (9.66)	42.22 (12.45)	2.113	.037*
PASAT – 2 seconds	37.33 (8.98)	33.07 (8.23)	2.537	.013**
CVLT-II-total recall	54.96 (9.96)	48.16(11.77)	3.384	.001**
CVLT-II –delayed recall	12.06 (2.74)	10.16 (4.02)	3.178	.002**
BVMT-R – total recall	22.14 (6.14)	20.10(7.61)	1.589	.115
BVMT-R – delayed recall	9.14 (2.05)	7.73 (3.18)	3.047	.003**
D-KEFS – Sorting	8.96 (2.47)	8.87 (2.57)	0.189	.850
D-KEFS – Description	31.82 (9.16)	31.37 (9.59)	0.266	.791
COWAT	43.08(11.02)	37.46 (13.77)	2.411	.017*
JLO	23.50 (4.66)	22.53 (5.42)	1.041	.300
SDMT without distractors	12.32 (1.72)	14.66 (3.65)	-4.904	<.001***
Other Cognitive Tests				
SDMT with distractors	13.12(1.80)	16.04(4.52)	-5.139	<.001***
Stroop without distractors	22.38 (5.70)	27.44 (9.36)	-3.813	<.001***
Stroop with distractors	23.88 (6.74)	30.20(11.22)	-3.991	<.001***

*$p < .05$ ** $p < .01$ *** $p < .001$

Key: WTAR – Wechsler Test of Adult Reading; HADS – Hospital Anxiety and Depressions Scale; EDSS – Expanded Disability Status Scale; PASAT – Paced Auditory Serial Addition Test; CVLT-II – California Verbal Learning Test, second edition; BVMT-R – Brief Visuospatial Memory Test- Revised; D-KEFS – Delis-Kaplan Executive Function System; COWAT – Controlled Oral Word Association Test; JLO – Judgement of Line Orientation Test; SDMT – Symbol Digit Modalities Test

D-KEFS description and the JLO tests, which assess executive functioning and visuospatial orientation. The chi-square tests revealed statistically significantly higher impairment rates among the RRMS participants on tests assessing information processing speed (i.e. PASAT, SDMT), verbal and visual learning and memory (i.e. CVLT-II and BVMT-R) and verbal fluency (i.e. COWAT). The tests that had the highest failure rate for the healthy controls were the PASAT – 2 (*n* = 9; 18%), the BVMT-R delayed recall (*n* = 6; 12%) and the SDMT (*n* = 6; 12%). These tests followed a similar pattern with the RRMS group, except with greater rates of failure with the SDMT, the largest number impaired at (*n* = 31; 39.2%) indicating it was the most sensitive test, followed by the PASAT – 2 (*n* = 28; 35.4%) and the BVMT-R delayed recall (*n* = 24; 30.4%).

Table 6.6

Frequencies and Percentages of Impairment on each of the MACFIMS Indices, the SDMT (with distractors) and the Stroop (with and without distractors)

	Healthy Control (*n* = 50)		Total RRMS (*n* = 79)			
	N	*%*	*N*	*%*	χ^2	*p*
PASAT – 3 seconds	4	8.0%	22	27.8%	7.496	.007**
PASAT – 2 seconds	9	18.0%	28	35.4%	4.555	.033*
Both PASAT tests	4	8.0%	20	25.3%	6.063	.014*
CVLT-II - Total	5	10.0%	22	27.8%	5.894	.015*
CVLT-II – delayed recall	3	6.0%	23	29.1%	10.165	.001**
BVMT-R – total recall	3	6.0%	17	21.5%	5.766	.016*
BVMT-R – delayed recall	6	12.0%	24	30.4%	5.982	.014*
D-KEFS – Sorting	4	8.0%	7	8.9%	0.029	.865
D-KEFS – Description	4	8.0%	6	7.6%	0.007	.933
COWAT	1	2.0%	17	21.5%	9.654	.002**
JLO	5	10.0%	13	16.5%	1.063	.303
SDMT without distractors	6	12.0%	31	39.2%	11.108	.001**
SDMT with distractors	3	6.0%	30	38.0%	16.444	<.001***
Stroop without distractors	4	8.0%	24	30.4%	9.024	0.003**
Stroop with distractors	3	6.0%	22	27.8%	9.355	0.002**

*$p < .05$ ** $p < .01$ *** $p < .001$

Key: PASAT – 3: Paced Auditory Serial Addition Test – 3 second; PASAT – 2: Paced Auditory Serial Addition Test – 2 second; CVLT-11: California Verbal Learning Test; BVMT: Brief Visual Learning Test-Revised; D-KEFS: Delis-Kaplan Executive Function System; COWAT: Controlled Oral Word Association Test; JLO: Judgment of Line Orientation; SDMT: Symbol Digit Modalities Test

Based on the global impairment designation (below a conventional 1.5 *SD* cut off on at least three of 11 MACIFMS tests), 41.77% of RRMS participants (*n* = 33) were classified as impaired in cognitive functioning. The remaining 58.23% RRMS participants (*n* = 46) were classified as cognitively intact. This divided the RRMS group into two subgroups, impaired RRMS and cognitively intact RRMS for the follow-up between-group analyses. Seven out of 50 healthy control participants (14%) were also considered cognitively impaired (Table 6.7). As was discussed in the pilot study section in the Methods chapter, the healthy control group did not have *a priori* testing assessing intact cognition. A similar inclusion and exclusion procedure was adopted when both the healthy control and RRMS groups were recruited. In the pilot study one out of ten of the participants tested as cognitively impaired or 10% of a small sample of ten. In the research study seven out of 50 or 14% of the healthy controls tested as impaired. Had the sample been larger it is possible that this sampling error would not have occurred. However, 42% of the RRMS sample tested as cognitively impaired, which was statistically significantly greater than the percentage of healthy controls who were impaired. The disparity between the groups on the assessment tests would likely have been even greater had there not been this small sampling error.

Table 6.7

Number of Healthy Control and RRMS Participants Impaired on MACIFMS Tests

	Group			
	Healthy Controls (*n* = 50)		Total RRMS (*n* = 79)	
	n	%	*n*	%
Impairment in <2 tests	35	70.00%	38	48.10%
Impairment in 2 tests	8	16.00%	8	10.13%
Impairment in 3 tests	3	6.00%	10	12.66%
Impairment in 4 or more tests	4	8.00%	23	29.11%

Table 6.7, shows the number of healthy controls compared to RRMS participants who were classified as impaired on the MACFIMS tests.

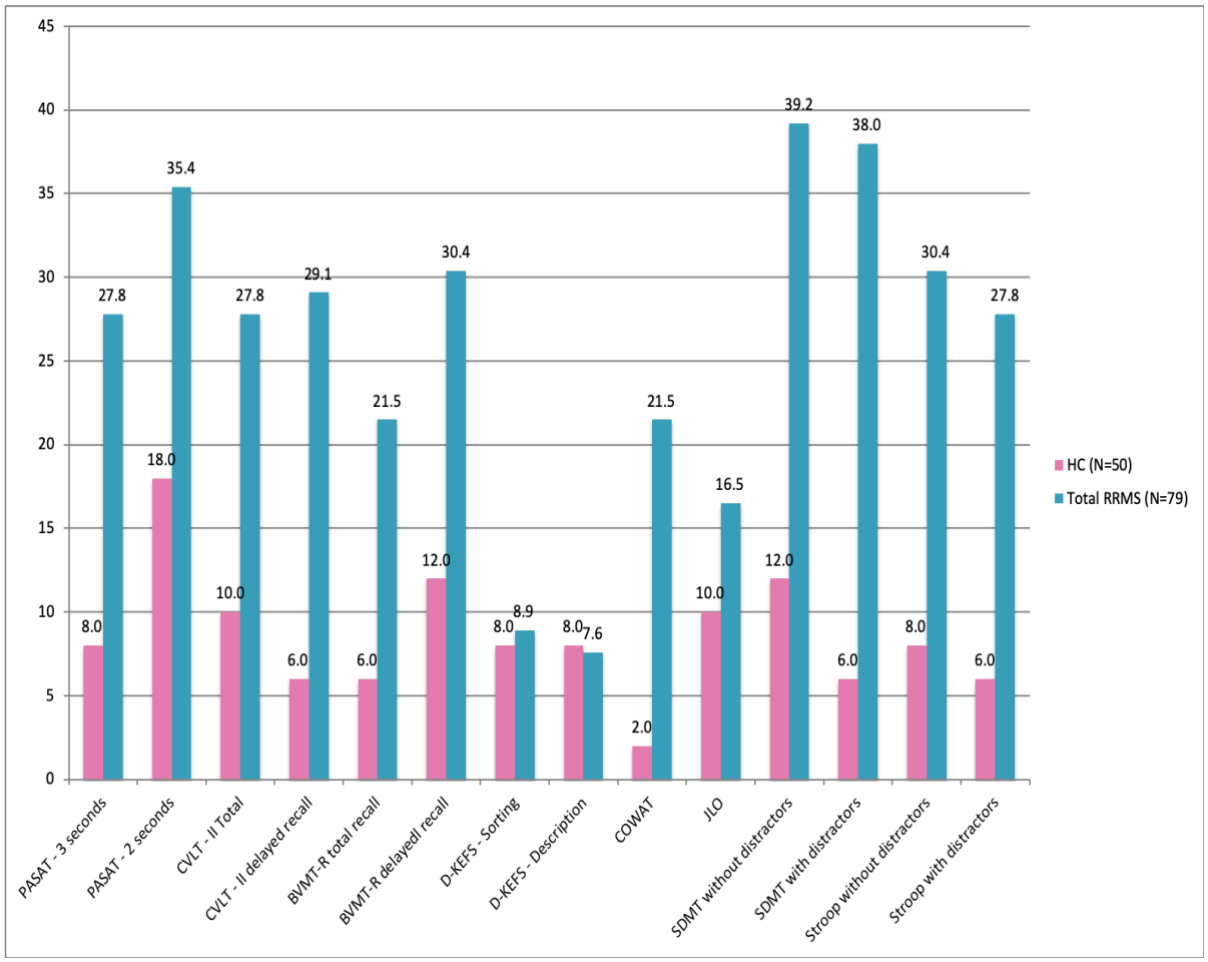


Figure 6.27

Impairment Rate in Percentages of the Healthy Controls (n = 50) and RRMS Total (n = 79) on the MACFIMS Tests, the SDMT (with distractors) and the Stroop (with and without distractors)

In Figure 6-27, a graph of the impairment rate between these two groups is illustrated. It can be clearly observed that the largest difference between the healthy control and RRMS

groups is in the SDMT reported as the most sensitive test of cognitive impairment in people with MS.

Receiver-operating-characteristic (ROC) Curve Analyses

Participants were separated into two groups, the cognitively impaired group and the cognitively RRMS group according to results on the MACFIMS battery. Receiver-operating-characteristic (ROC) curve analyses were calculated for each test in relation to the previously mentioned classification of impaired versus intact RRMS groups. The area under the ROC curve (AUC) shows how well each of the MACFIMS subtests was able to discriminate between those participants who were impaired and those who were intact. Visually, the AUC appears as a plot of sensitivity, or the test's ability to correctly identify those that have an outcome of interest on the y-axis and 1 – specificity on the x-axis, where specificity is defined as the test's ability to correctly identify those who do not have the outcome of interest. The x-axis is written as a 1 negative (1-specificity), because it is a false positive fraction. The diagonal line on the plot of ROC values going from the bottom left corner to the top right corner signifies an AUC value of 0.5. This would not be of any value to the researcher as it is essentially equivalent to a coin flip in its ability to discriminate among outcome categories. The best tests are the ones that maximize both sensitivity and specificity and result in a high AUC value (Fawcett, 2006). This high value would be represented by a line that is closest to the top left corner of the ROC plot.

Figure 6.28 shows the ROC curves for all of the tests except the SDMT (which has different classification criteria). ROC curve analyses were also presented for the Stroop (without distractors) and then the SDMT (with distractors) and the Stroop (with distractors) to

ascertain whether distractors increased the predictive value of impaired versus intact participants.

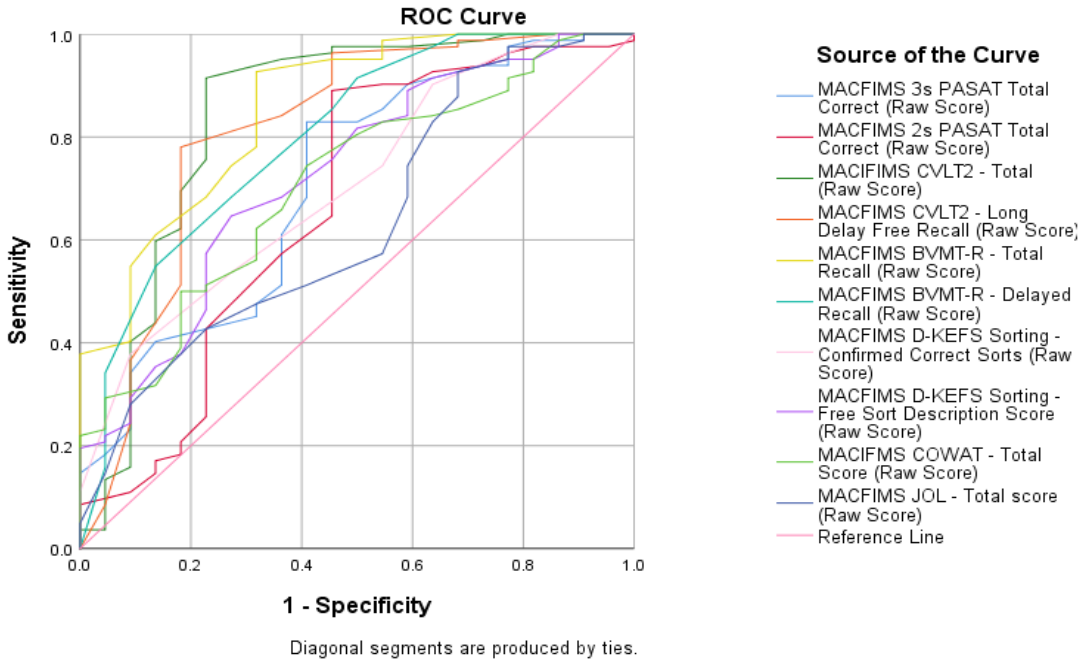


Figure 6.28

ROC Curve Analyses for MACFIMS Subtests Excluding SDMT at 95% Confidence Interval for the Area under the Curve

The test with the highest AUC was the BVMT-R – total recall, which had an AUC value of 0.86 with a 95% confidence interval (CI) of 0.77-0.95. The confidence interval indicates that there is 95% confidence that the true AUC value for the BVMT-R – total recall lies between 0.77 and 0.95. AUC values between 0.8-0.9 are considered excellent discrimination and the BVMT-R – total recall AUC value of 0.86 indicated that this test correctly classified randomly drawn pairs of impaired/intact 86% of the time. The test with the second highest AUC was the CVLT-II-total with an AUC of 0.84, 95% CI 0.72-0.96. This was followed by the SDMT (without distractors) with AUC=0.82 (95% CI 0.72-0.92), the CVLT-

II –delayed recall with AUC=0.81 (95% CI 0.69-0.93), the CVLT-II –delayed recall with AUC=0.81 (95% CI 0.69-0.93), the BVMT-R – delayed recall with AUC=0.80 (95% CI 0.69-0.91), the D-KEFS – Description with AUC = 0.73 (95% CI 0.61-0.85), the D-KEFS – Sorting with AUC = 0.71 (95% CI 0.59-0.83), the COWAT with AUC = 0.71 (95% CI 0.59-0.83), the PASAT – 3 seconds with AUC = 0.71 (95% CI 0.58-0.84), the PASAT – 3 seconds with AUC = 0.67 (95% CI 0.53-0.82), and finally the JLO with AUC = 0.63 (95% CI 0.50-0.77).

Figure 6.29 shows the high discrimination of the SDMT (without distractors) with an AUC value of 0.82 (95% CI 0.72 - 0.92). This lies below the BVMT-R – total recall (AUC – 0.86) and CVLT-II-total (AUC = 0.84).

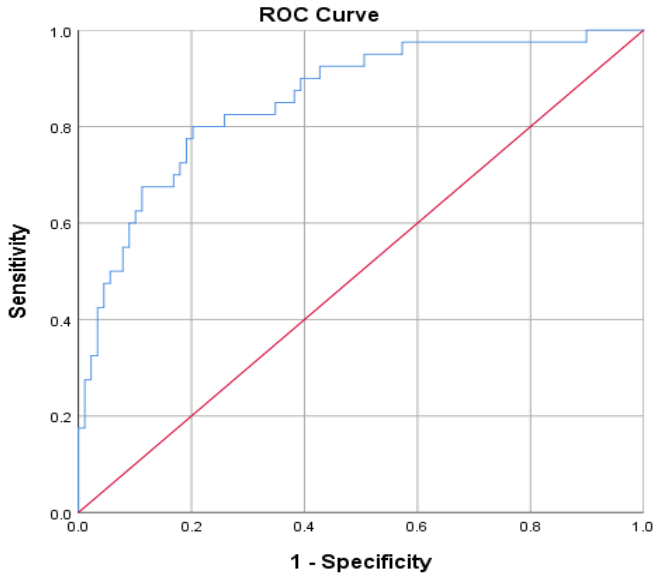


Figure 6.29

ROC Curve Analyses for the SDMT (without distractors) at 95% Confidence Interval for the Area under the Curve, with SDMT lying at 0.82 (0.72-0.92)

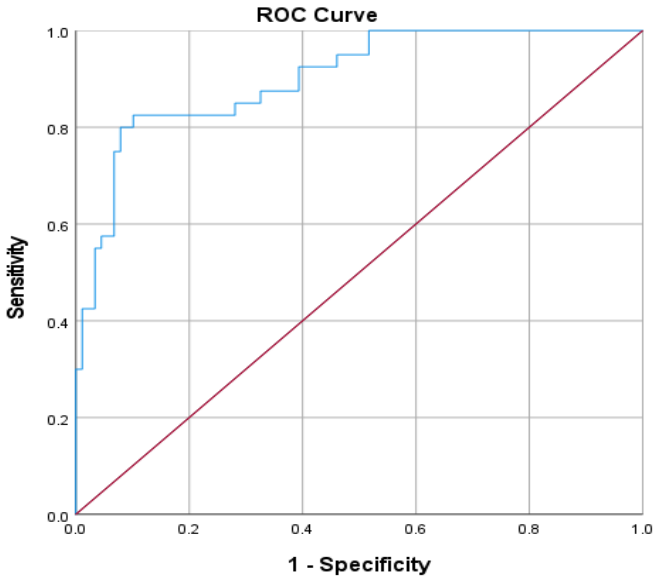


Figure 6.30

ROC Curve Analyses for the SDMT (with distractors) at 95% Confidence Interval for the Area under the Curve

A ROC curve analysis was also conducted for SDMT (with distractors) as seen in Figure 6.30. The SDMT (with distractors) had a higher level of AUC than the SDMT without distractor (the SDMT with distractors): AUC = 0.90, 95% CI: 0.85 – 0.96, $p < .001$; the SDMT (without distractors); AUC = 0.82, (95% CI: 0.72 - 0.92, $p < .001$), indicating a particularly high level of diagnostic accuracy (AUC = 0.90) in detecting cognitive impairment. This result is pivotal in ascertaining an answer to the research question. It is noteworthy that this score was higher than the two tests, the BVMT-R – total recall and CVLT-II-total on the MACFIMS, which had the highest level of discrimination between the healthy controls and RRMS participants on the MACFIMS composite.

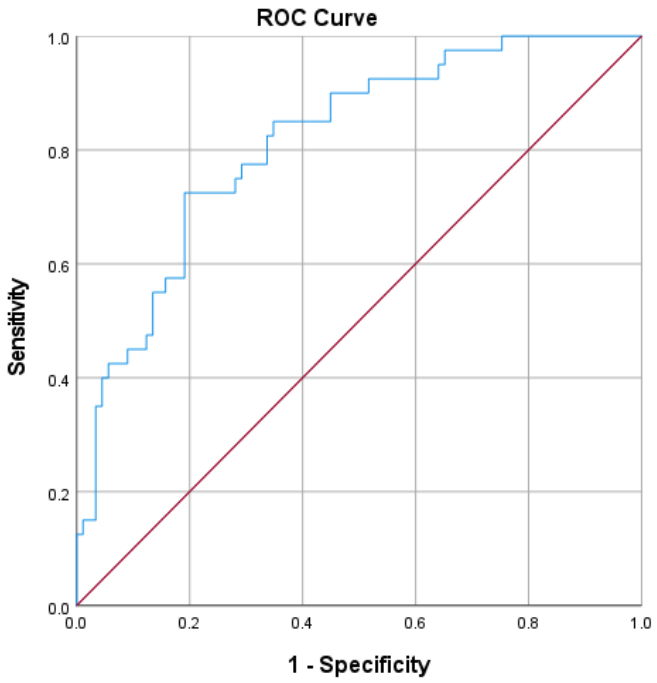


Figure 6.31

ROC Curve Analyses for the Stroop (without distractors), at 95% Confidence Interval for the Area under the Curve

The ROC curve analysis conducted for the Stroop (without distractors) and the corresponding AUC in Figure 6.31 illustrates that the Stroop had good predictive ability to discriminate global impairment from the healthy control participants (AUC = 0.82, 95% CI: 0.74 – 0.89, p < .001). This is the same AUC value as the SDMT (without distractors).

The Stroop (with distractors) as seen in Figure 6.32 had a similar level of AUC as the Stroop (without distractors). The values were the Stroop (with distractors): AUC = 0.81, 95% CI = 0.72-0.89, *p* < .001 and the Stroop without distractors: AUC = 0.82, 95% CI: 0.74 – 0.89, *p* < .001), which revealed that the diagnostic accuracy of impairment did not improve when distractors were added to the Stroop.

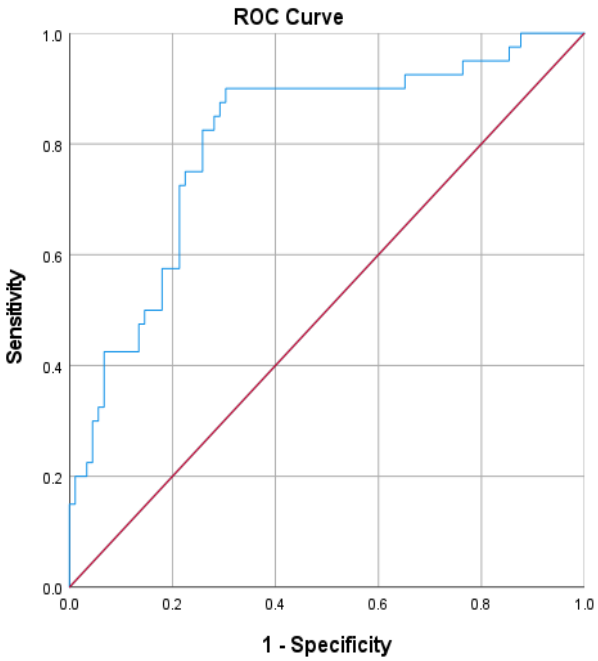


Figure 6.32

ROC Curve Analyses for the Stroop (with distractors) at 95% Confidence Interval for the Area under the Curve

In sum, Table 6.8 shows the AUC values and their associated 95% confidence intervals. The *p*-values demonstrate that each test was significantly higher than the AUC value of 0.5 represented by the diagonal line. The JLO had the least *p*-value and thus had the lowest ability to discriminate cognitively impaired from cognitively intact participants, being right at the significance threshold with $p = .05$. The SDMT (with distractors) showed the highest discriminant ability with an AUC value of 0.90 with significance value $p <. 001$. This supports the literature that identifies the SDMT as being highly sensitive to cognitive impairment

(Benedict et al., 2012; Brochet et al., 2008; Drake et al., 2010; Gromisch et al., 2018; Parmentier, Weinstock-Guttmann et al., 2007; Sheridan, et al., 2006; Sonder et al., 2013).

Table 6.8

ROC Analyses of the 11 MACFIMS Subtest, SDMT (with distractors) and the Stroop (with and without distractors)

Test Result Variable(s)	AUC	95% CI	*p*
PASAT – 3 seconds	0.71	0.58-0.84	.003**
PASAT – 2 seconds	0.67	0.53-0.82	.014*
CVLT-II-total	0.84	0.72-0.96	<.001***
CVLT-II –delayed recall	0.81	0.69-0.93	<.001***
BVMT-R – total recall	0.86	0.77-0.95	<.001***
BVMT-R – delayed recall	0.80	0.69-0.91	<.001***
D-KEFS – Sorting	0.71	0.59-0.83	.003**
D-KEFS – Description	0.73	0.61-0.85	.001**
COWAT	0.71	0.59-0.83	.003**
JLO	0.63	0.50-0.77	.053
SDMT without distractors	0.82	0.72-0.92	<.001***
SDMT with distractors	0.90	0.85-0.96	<.001***
Stroop without distractors	0.82	0.74-0.89	<.001***
Stroop with distractors	0.81	0.72-0.89	<.001***

*$p < .05$, ** $p < .01$, *** $p < .001$

Key: PASAT – 3: Paced Auditory Serial Addition Test – 3 second; PASAT – 2: Paced Auditory Serial Addition Test – 2 second; CVLT-11: California Verbal Learning Test; BVMT: Brief Visual Learning Test-Revised; D-KEFS: Delis-Kaplan Executive Function System; COWAT: Controlled Oral Word Association Test; JLO: Judgment of Line Orientation; SDMT: Symbol Digit Modalities Test

Group Comparisons Between Cognitively Intact RRMS and Cognitively Impaired RRMS Participants

The between-group statistics comparing the cognitively intact RRMS (n = 46) and the impaired RRMS (n = 33) groups are displayed in Table 6.9. Demographic comparisons between the groups revealed that the impaired group was significantly older than the intact group, had MS for a significantly longer duration, and obtained significantly higher EDSS and WTAR scores.

Based on chi-square tests, there was no significant difference between the proportion of females and level of employment between groups. There were 35 females in the intact RRMS samples representing 76.08% of this group compared to 20 females in the impaired RRMS samples representing 60.61% of that sample. A slightly lower (but not significantly different) proportion of the intact RRMS sample was unemployed, 17 (51.52%) compared to the impaired RRMS group 18 (39.13%). No statistically significant differences based on independent samples *t*-test were found between the intact RRMS group and the impaired RRMS group on years of education or HADs scores.

On the MACIFMS tests (Table 6.9), the intact RRMS group obtained significantly better scores than the impaired RRMS on all 11 tests according to the results of independent samples *t*-tests. The intact RRMS group had statistically significantly higher scores than the impaired group on the PASAT – 3 seconds, the PASAT – 2 seconds, the CVLT-II-total and delayed recall, the BVMT-R – total recall and delayed recall, the D-KEFS – Sorting and Description, the COWAT and the JLO. Additionally, the intact group took a significantly shorter time to complete the SDMT (without distractors) than the impaired RRMS group.

With regard to the additional cognitive tests included in this study (Table 6.9), results on the SDMT (with distractors) and the Stroop (with and without distractors) revealed that the impaired RRMS group took significantly longer time to complete all three tests, as compared to the intact RRMS cohort. Independent sample *t*-tests also indicated that the impaired RRMS group made a significantly higher number of errors on the SDMT and Stroop than the intact RRMS group. The mean values were greater in the impaired RRMS group as compared to those in the intact RRMS groups. These findings confirm the criterion validity of the MACFIMS battery and its discriminating power in cognitive performance in people with MS.

Table 6.9

Intact RRMS and Impaired RRMS Between-Group Statistics for Demographic Characteristics, MACFIMS, SDMT and Stroop (n=79)

	Groups			
	Intact RRMS *n* = 46	Impaired RRMS *n* = 33	*t*-test/ χ^2	
Characteristics	Mean (*SD*)	Mean (*SD*)		*p*
Age, years	40.72(9.41)	45.88(8.29)	-2.525	.014*
Female sex — *n*(%)	35 (76.08%)	20 (60.61%)	χ2=2.177	.140
Education, years	15.80(2.19)	15.09 (2.21)	1.420	.160
Employment — *n*(%)				
Employed	28 (60.87%)	16 (48.48%)	χ2=1.194	.274
Unemployed	18 (39.13%)	17 (51.52%)		
Duration of RRMS, years	10.50 (6.04)	14.36 (8.43)	2.211	.031*
EDSS score	1.63 (1.16)	2.61 (1.59)	-2.981	.004**
WTAR score	38.70 (4.26)	34.13 (5.46)	4.076	<.001***
HADS score				
Anxiety	10.48 (4.22)	9.76 (3.95)	0.770	.444
Depression	6.93 (3.54)	8.18 (3.61)	-1.531	.130
Total	17.41 (6.75)	17.94 (6.71)	-0.343	.733
MACFIMS				
PASAT – 3 seconds	47.83 (8.45)	32.31(12.33)	5.703	<.001***
PASAT – 2 seconds	34.89 (7.54)	27.94 (8.13)	3.103	.003**
CVLT-II-total	55.17 (6.95)	38.39 (7.54)	8.776	<.001***
CVLT-II –delayed recall	12.57 (2.62)	6.82 (3.17)	8.806	<.001***
BVMT-R – total recall	24.30 (5.78)	14.06 (5.62)	7.783	<.001***
BVMT-R – delayed recall	9.30 (1.92)	5.47 (3.29)	5.927	<.001***
D-KEFS – Sorting	9.96 (2.13)	7.36 (2.40)	5.066	<.001***
D-KEFS – Description	35.52 (8.32)	25.58 (5.23)	5.276	<.001***
COWAT	43.33 (14.20)	29.45 (8.04)	5.469	<.001***
JLO	24.70 (3.61)	19.52 (6.11)	4.352	<.001***
SDMT without distractors	12.87 (2.19)	17.16 (3.83)	-5.793	<.001***
Other Cognitive Tests				
SDMT with distractors	13.53(2.30)	19.55(4.56)	-6.978	<.001***
Stroop without distractors	23.51(6.47)	32.91 (10.07)	-5.047	<.001***
Stroop with distractors	25.58 (7.09)	36.62 (12.76)	-4.495	<.001***
Errors on SDMT and Stroop				
Errors on SDMT without distractors	Mean Rank = 34.82	Mean Rank=45.88	z=-2.296	.022*
Errors on SDMT with distractors	Mean Rank = 31.82	Mean Rank =51.41	z=-4.204	<.001***
Errors on Stroop without distractors	Mean Rank =36.62	Mean Rank =44.71	z=-2.323	.020*
Errors on Stroop with distractors	Mean Rank =35.67	Mean Rank =46.03	z=-2.892	.004**

*p < .05, ** p < .01, *** p < .001

Key: WTAR – Wechsler Test of Adult Reading; HADS – Hospital Anxiety and Depression Scale; EDSS – Expanded Disability Status Scale; PASAT – Paced Auditory Serial Addition Test; CVLT-II – California Verbal Learning Test, second edition; BVMT-R – Brief Visuospatial Memory Test- Revised; D-KEFS – Delis-Kaplan Executive Function System; COWAT – Controlled Oral Word Association Test; JLO – Judgement of Line Orientation Test; SDMT – Symbol Digit Modalities Test

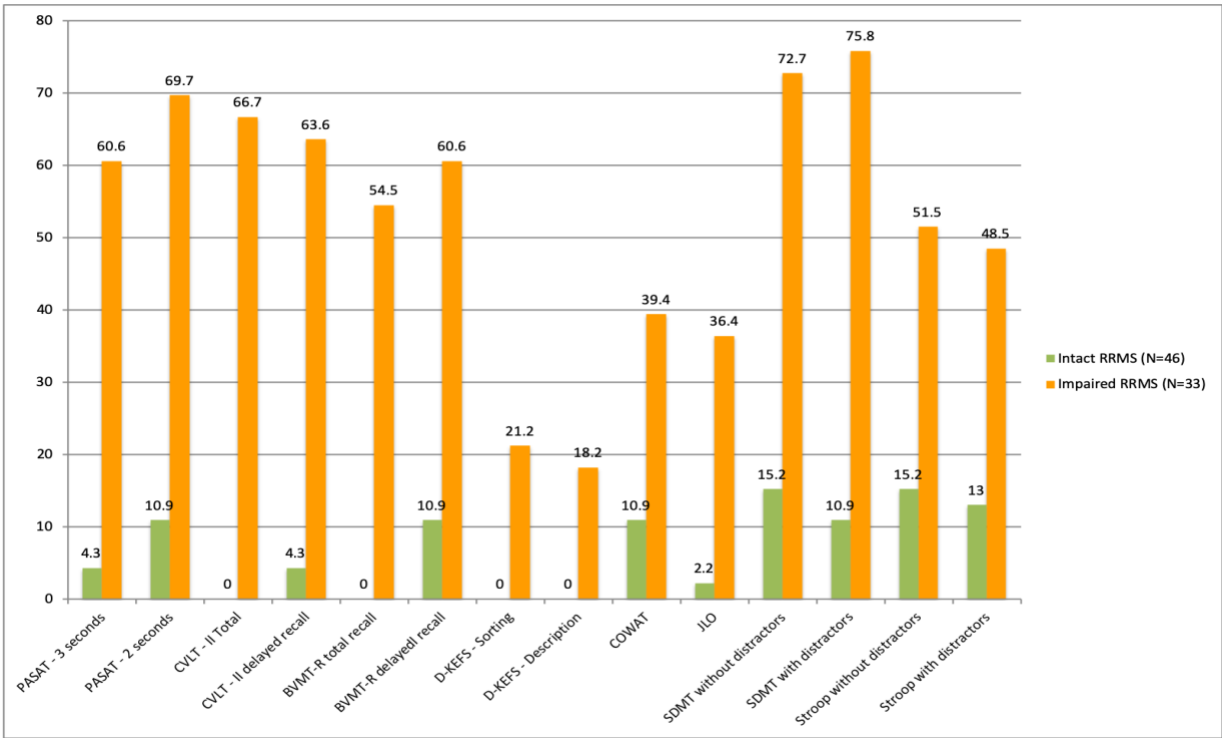


Figure 6.33

Impairment Rate in Percentages of the Intact RRMS (n = 46) and Impaired RRMS (n = 33) on the MACFIMS, the SDMT (with distractors) and the Stroop (with and without distractors)

The impairment rate in percentages comparing the intact RRMS and impaired RRMS groups can clearly be seen in Figure 6.33. The latter group is significantly impaired on all the tests compared to the intact group, with the largest differences on the SDMT (with distractors) followed by the SDMT (without distractors). The cognitive strength of the intact RRMS is noticeable as well, with no failure on four of the tests and a low rate of impairment on all the other tests. Marginally higher rates of impairment were visible on the SDMT (without distractors) and the Stroop (with and without distractors) The number of errors made on the

four tests, the SDMT (with and without distractors) and the Stroop (with and without distractors) were also compared between the two groups, cognitively intact RRMS and impaired RRMS. Independent-samples Mann-Whitney U tests were conducted for the four variables measuring errors between the groups. The Mann-Whitney U test was used as the non-parametric option to the independent-samples *t*-test, as the data from the error scores were not normally distributed. This was assessed by visual inspection of the histogram portraying the error scores (see Figures 6.23 to 6.26 in Appendix J). The distributions of the four error variables were skewed to the right as many participants made zero errors. The Mann-Whitney test statistics indicated that the numbers of errors on the four tests made by the cognitively intact RRMS participants all differed significantly from those of the impaired group (Figures 6.34 to 6.37 in Appendix K).

Figure 6.34 shows the distribution of the number of errors on the SDMT (without distractors) and Figure 6.35 for the SDMT (with distractors) for the intact RRMS and the impaired RRMS sample. The distributions were not similar, as assessed by visual inspection, with the impaired group having fewer participants that made no errors, and several participants with a higher number of errors than the intact group. Figure 6.36 depicts the distribution of the number of errors on the Stroop (without distractors) and Figure 6.37 the Stroop (with distractors) for intact RRMS and impaired RRMS sample. Once again, a similar pattern is observed, the distributions were not similar, and the intact group had fewer errors compared the impaired group.

Global Impairment Based on Two Criteria

In the Methods chapter, the description of the research design noted that the SDMT and the Stroop were administered twice within a two-hour period. This introduced the

possibility that practice effects could affect results. Consequently, a counterbalance methodology was utilized in an attempt to mitigated the potential confounding effects of the two administrations. In addition, instead of using failure on three or more of the 11 MACFIMS tests as a cutoff for determining impairment (Criterion 1), the SDMT was excluded from the indices of the MACFIMS in order to assess its impact. This resulted in a different criterion of failing three or more of the remaining 10 MACIFMS indices (Criterion 2) for defining global impairment. The raw score cut-offs previously established using the -1.5 SD criterion were applied. Based on these revised criteria, the constituent numbers in the RRMS group changed. The intact RRMS group contained 51 members, five more than in the previous group (n = 46) while there were 28 in the impaired RRMS compared to 33 when Criterion 1 was implemented. The results are shown in Table 6.10.

Table 6.10

The Number of Globally Intact and Globally Impaired Participants as Defined by Two Global Impairment Criteria

		Criterion 2 **		
		Intact	Impaired	Total
Criterion 1*	Intact	46	0	46
	Impaired	5	28	33
	Total	51	28	79

*Criterion 1: Global Impairment (failing 3 out of 11)
**Criterion 2: Global Impairment (failing 3 out of 10)

The sensitivity and specificity of the MACFIMS subtests, the SDMT (with distractors) and the Stroop (with and without distractors) in detecting global cognitive impairment when using the two sets of criteria are shown in Table 6.11. The SDMT had the highest sensitivity among all 14 tests (67.5%) in detecting global impairment using Criterion 1. When auditory distractors were added to the SDMT, sensitivity remained the same and specificity increased

from 88.8% to 93.3%. When the auditory distractors were added to the Stroop the sensitivity diminished from 45% to 42.5%, however the specificity increased from 88.8% to 91%.

Table 6.11

Sensitivity and Specificity of the MACFIMS Subtests, the SDMT and Stroop test in Detecting Global Cognitive Impairment

	Global Impairment (failing 3/11)			
	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
MACFIMS				
PASAT – 3 seconds	55.0%	95.5%	84.6%	85.2%
PASAT – 2 seconds	65.0%	87.6%	70.3%	84.8%
CVLT-II- total	60.0%	96.6%	88.9%	84.3%
CVLT-II –delayed recall	57.5%	96.6%	88.5%	83.5%
BVMT-R – total recall	50.0%	98.9%	95.2%	81.5%
BVMT-R – delayed recall	60.0%	92.1%	77.4%	83.7%
D-KEFS – Sorting	25.0%	98.9%	90.9%	74.6%
D-KEFS – Description	22.5%	98.9%	90.0%	73.9%
COWAT	35.0%	93.3%	70.0%	76.1%
JLO	37.5%	96.6%	83.3%	77.5%
SDMT without distractors	67.5%	88.8%	73.0%	85.9%
Other Cognitive Tests				
SDMT with distractors	67.5%	93.3%	81.8%	86.5%
Stroop without distractors	45.0%	88.8%	64.3%	78.2%
Stroop with distractors	42.5%	91.0%	68.0%	77.9%

Key: PASAT – 3: Paced Auditory Serial Addition Test – 3 second; PASAT – 2: Paced Auditory Serial Addition Test – 2 second; CVLT-11: California Verbal Learning Test; BVMT: Brief Visual Learning Test-Revised; D-KEFS: Delis-Kaplan Executive Function System; COWAT: Controlled Oral Word Association Test; JLO: Judgment of Line Orientation; SDMT: Symbol Digit Modalities Test

When Criterion 2 (failure of three out of 10), was used the SDMT was removed from the indices to define global impairment. The newly constituted groups of intact RRMS (*n* = 51), impaired RRMS (*n* = 28) and healthy control (n = 50) then became the subject of the following analyses.

Group Comparison on Processing Speed as Measured on the SDMT and Stroop Descriptive Differences between Processing Speed on the SDMT (with and without distractors)

As shown in Table 6.12, the processing speed performance of all groups, the healthy control group (n = 50), the intact RRMS group (n = 51) and the impaired RRMS group (n = 28) increased significantly on the SDMT when auditory distractors were introduced. The results revealed that the impaired RRMS group had the largest difference in processing speed between the two tasks. The model showed that the processing speed of the SDMT (with distractors) in the impaired RRMS group was 2.47 seconds (SE = 0.63 seconds) longer on average than that of the SDMT (without distractors). The healthy control group had the second largest difference in processing speed between the two tasks, revealing that the processing speed of the SDMT (with distractors) in the healthy control group was 0.80 seconds (SE = 0.16 seconds) longer on average than that of the SDMT (without distractors). The intact RRMS group had a marginally smaller difference in processing speed between the two tasks with 0.79 seconds (SE = 0.23) longer on average than that of the SDMT (without distractors). The changes for the three groups over the two tasks are depicted in Figure 6.37 (Appendix K).

The SDMT with distractors took longer to process for all groups. Figure 6.38 illustrates the degrees of change in processing time across three groups between the two tasks, with the largest change in time to process the task notable in the impaired RRMS group. Processing time changes of the healthy controls and cognitively intact RRMS groups were less pronounced, however time increased for both of these groups similarly.

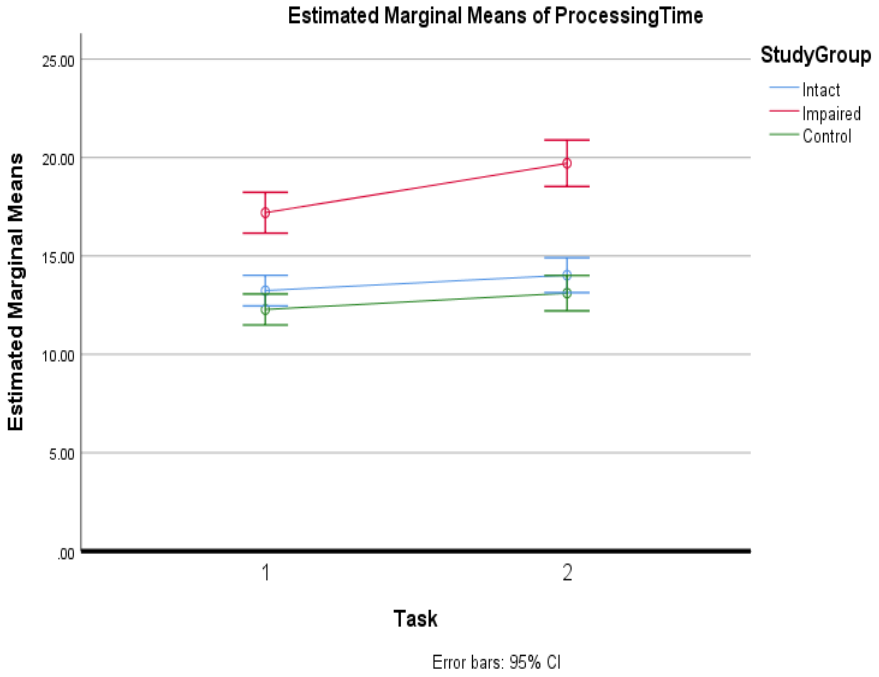
Table 6.12

Within Group Comparison on Processing Speed of the SDMT (with and without distractors)

n = 129

Group		Task		Pairwise Comparisons between Tasks			
		SDMT without Distractors	SDMT with Distractors	Estimate	SE	*t* value	*p*
Healthy Control (*n* = 50)	M	12.32	13.12	-0.831	0.162	-5.120	<.001***
	(*SD*)	(1.72)	(1.80)				
Intact RRMS (*n* = 51)	M	13.25	14.04	-0.785	0.234	-3.350	.002**
	(*SD*)	(2.40)	(2.76)				
Impaired RRMS (*n* = 28)	M	17.24	19.71	-2.514	0.623	-4.020	<.001***
	(*SD*)	(4.14)	(4.86)				

Note: values are in seconds
** $p < .001$
*** $p < .001$



Task 1: SDMT without distractors; Task 2: SDMT with distractors
Covariates appearing in the model are evaluated at the following values: Current Age = 42.3770, Sex = 1.6967, Employed or not = 1.3361, Years of Education = 15.4426, HADS - Anxiety (Raw Score) = 7.8525, HADS - Depression (Raw Score) = 5.4918, WTAR - Total Score (Raw Score) = 36.6967, Distracters condition administered first or second = 1.508

Figure 6.38

Plot of Estimated Marginal Means across Three Groups with 95% CI Bars

Repeated measures analyses of variance (RANCOVA) on processing speed as measured on the SDMT

To analyze whether the change in processing speed on the SDMT was the result of an interaction between the groups (healthy controls, intact and impaired RRMS) and tasks (the SDMT with and without distractors), a two-way-repeated measures analysis of covariance (RANCOVA) was conducted while controlling for eight study design demographic and disease related variables. These covariates included counterbalance, age, gender, employment status, years of education, HADS anxiety score, HADS depression score and WTAR score, which could all potentially influence the outcome.

The RANCOVA results (see Table 6.13) revealed that there was a statistically significant interaction between group and task on the SDMT processing speed, F (2,119) = 8.000, $p < .001$, partial $\eta^2 = 0.081$. To understand the nature of the interaction term, separate models by group were run to assess the relationship between the processing speed of two tasks, the SDMT (with and without distractors). Each of the three separate models controlled for the same variables as in the initial model. Simple main effects were also calculated. Processing speed on the SDMT (without distractors) was not statistically significantly different in the healthy control group as compared to the cognitively intact RRMS group, $t = 1.219$, $p = .226$, partial $\eta^2 = .0.013$, mean difference of 0.916 [95% CI, -0.574 to 2.406]. A similar result followed with the processing speed of the SDMT (with distractors), which was also not significantly different in the healthy control group as compared to the intact RRMS group, $t = 0.570$, $p = 0.570$, partial $\eta^2 = 0.003$, mean difference of 0.487 [95% CI, -1.206 to 2.180]. However, processing speed on the SDMT (without distractors) was significantly faster in the healthy control group as compared to the impaired RRMS group, $t = 5.429$, $p < 0.001$, partial $\eta^2 = 0.210$, with a mean difference of 4.626 [95% CI, 2.938 to 6.315]. Additionally, processing

speed on the SDMT with distractors was also significantly faster in the healthy control group compared to the impaired RRMS group, $t = 5.833$, $p < .001$, partial $\eta^2 = 0.235$, with a mean difference of 5.647 (95% CI, 3.728 to 7.565).

The only covariate that was statistically significant was highest level of education, F(1,119)=4.772, p=0.031, $\eta^2_{partial}$= 0.041. The other covariates (counterbalance, age, gender, employment status, HADS anxiety and HADS depression, WTAR) entered into the model were non-significant in relation to the SDMT processing speed.

Table 6.13

Model Statistics for the Two Factors, Group and Task, with the SDMT Processing Speed (in seconds) as Dependent Variable (n = 129)

	Model Statistics			
	F	*p*	$\eta^2_{partial}$	Power((1-β)
Main effects				
Group	22.875	<.001***	0.292	1
Task	56.30	<.001***	0.026	.395
Group * Task	8.000	<.001***	0.081	.797
Covariates				
Counterbalance	0.069	.793	0.001	.058
Age	0.086	.769	0.001	.06
Gender	1.575	.212	0.014	.238
Employment	1.232	.269	0.011	.196
Education	4.772	.031*	0.041	.581
HADS Anxiety Score	0.075	.784	0.001	.059
HADS Depression Score	0.005	.942	0	.051
WTAR Score	0.034	.855	0	.054

*$p < .05$
** $p < .01$
*** $p < .001$
Key: WTAR – Wechsler Test of Adult Reading; HADS – Hospital Anxiety and Depression Scale

Descriptive differences between processing speed on the Stroop (without and with distractors)

The same analyses that were undertaken on the SDMT were implemented with the Stroop (with and without distractors). Similar to the results obtained for the SDMT, time of processing speed significantly increased for all of the groups, the healthy control (n = 50), the cognitively intact RRMS (n = 51) and cognitively impaired RRMS (n = 28) groups when auditory distractors were introduced. It was originally hypothesized that that the addition of distractors to the SDMT and Stroop would result in slower processing speed and the results do uphold this thesis.

As shown in Table 6.14 all groups took longer to complete the Stroop with distractors. The healthy controls had the smallest variation in difference in processing speed between the between the two tasks Stroop (with and without distractors), with a mean difference of 1.50 seconds (SE =0.465). This was followed by the cognitively intact RRMS group with a mean difference of 2.32 seconds (0.566). Lastly the impaired RRMS group with the largest disparity in processing speed with a mean difference 3.55 seconds (SE = 1.092) longer over the Stroop with distractors.

Figure 6.39 illustrates the change in processing time across three groups on the Stroop with distractors, between the two tasks. The processing time for the three groups increased, with the largest change in time to process the task notable in the impaired RRMS group. Processing time changes of the healthy controls and cognitively intact RRMS groups were less manifest, but time increased for both of these groups.

Table 6.14

Within Group Comparisons on Processing Speed of the Stroop with and without Distractors (n =129)

		Task		Pairwise Comparisons between Tasks			
Group		Stroop without distractors	Stroop with distractors	Estimate	*SE*	*t* value	*p*
Healthy Control	M (SD)	22.38 (5.70)	23.88 (6.74)	-1.440	0.465	-3.100	.003**
Intact RRMS	M (SD)	24.34 (7.33)	26.66 (8.26)	-2.303	0.566	-4.070	<.001***
Impaired RRMS	M (SD)	33.08 (10.12)	36.63 (13.08)	-3.647	1.092	-3.340	.003**

Note: values are in seconds
*$p < .05$
** $p < .01$
*** $p < .001$

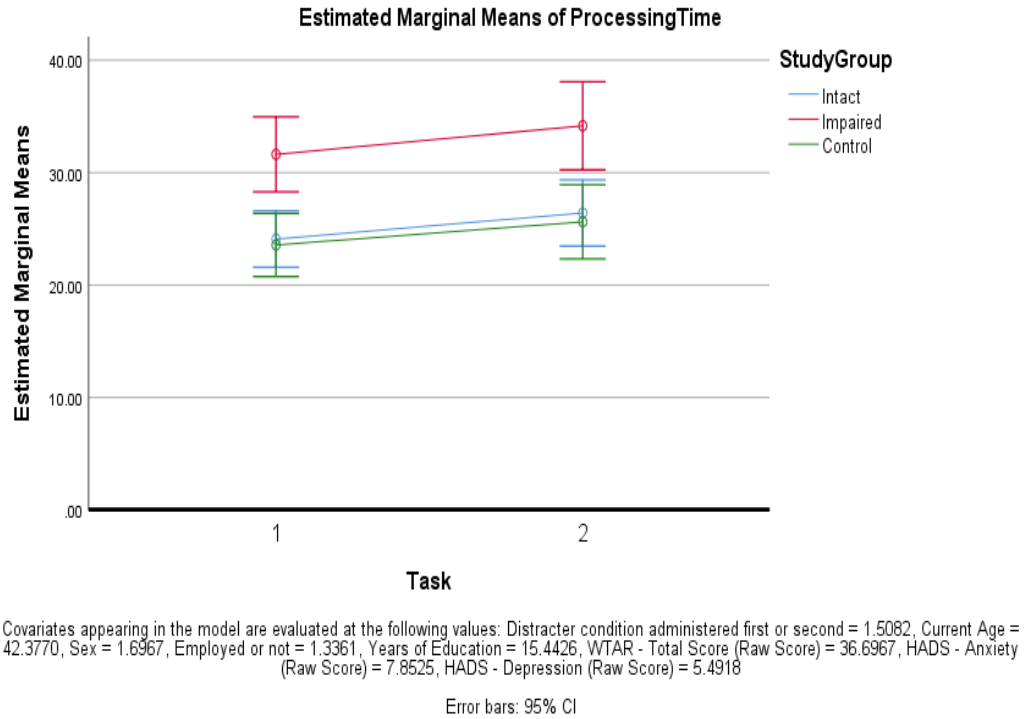


Figure 6.39

Plot of Estimated Marginal Means across Three Groups with 95% CI Bars

Repeated measures analyses of covariance (RANCOVA) on processing speed as measured on the Stroop

To analyze whether the change in processing speed on the Stroop was the result of an interaction between the groups (healthy control, intact RRMS and impaired RRMS) and tasks (the Stroop with and without distractors), a two-way repeated measures RANCOVA analysis was conducted while controlling for the same eight variables used in the model in the previous section (i.e. counterbalance, age, gender, employment status, years of education, HADS anxiety score, HADS depression score and WTAR score).

There was no statistically significant interaction (see Table 6.15) between task and group on the Stroop processing speed ($F(2,119) = 2.45$, $p = .09$). A larger sample size would be useful to better understand this relationship, but from a purely exploratory standpoint,

Table 6.15

Model Statistics for the Two Factors, Group and Task, with the Stroop Processing Speed (in seconds) as Dependent Variable (n = 129)

	Model Statistics			
	F	*p*	η^2 partial	Power(1-β)
Main effects				
Group	7.326	.001**	0.117	.933
Task	40.5	<.001***	0.052	.685
Group * Task	2.45	.090	0.001	.061
Covariates				
Counterbalance	0.491	.485	0.004	.107
Age	0.591	.444	0.005	.119
Gender	0.057	.811	0.001	.056
Employment	0.162	.688	0.001	.068
Education	2.31	.131	0.020	.325
HADS Anxiety Score	2.83	.095	0.025	.385
HADS Depression Score	1.227	.270	0.011	.195
WTAR Score	0.018	.894	0	.052

*$p < .01$
** $p < .001$
Key: WTAR – Wechsler Test of Adult Reading; HADS – Hospital Anxiety and Depression Scale

separate models were run by group to assess any possible relationship between the two tasks. Each of the three separate models controlled for the same variables as in the starting model.

The results indicate that the cognitively impaired RRMS group had the largest difference in processing speed between the two versions of the Stroop (i.e. with and without distractors), as the adjusted mean on the Stroop with distractors was 3.65 seconds (*SE* = 1.09 seconds) longer on average than that of the same test without distractors. The cognitively intact RRMS group had the second largest difference in processing speed between the two versions of the test, with the adjusted mean of the Stroop with distractors being 2.30 seconds (*SE* = 0.57 seconds) longer on average than that of the Stroop with no distractors. The healthy control group had the smallest difference in processing speed between the two versions of the test, as the adjusted mean of processing speed to the Stroop with distractors was 1.44 seconds longer (*SE* = 0.47 seconds) on average than that of the Stroop with no distractors. None of the eight covariates (counterbalance, age, gender, employment status, HADS anxiety and HADS depression, WTAR) entered into the model were significant.

Group Comparison on Errors Scores of the SDMT and the Stroop

The Shapiro-Wilk statistic revealed that errors scores obtained on the SDMT and the Stroop Test were not normally distributed, necessitating the use of non-parametric statistics for bivariate analyses. Data that is in the form of counts or rates (as for error scores) do not typically follow a normal distribution, which is why Poisson regression models are more suitable than linear regression models to assess multivariable relationships with such data. Consequently, Poisson regressions were conducted to assess differences between groups (healthy controls, RRMS intact and RRMS impaired) and across task (without and with distractors) using the count of errors as a dependent variable with the same eight variables as in the previous section as covariates was conducted

Descriptive differences between the number of errors on the SDMT without and with distractors

The breakdown on the number of errors on the SDMT by group and task is depicted in Table 6.16. The healthy control group had a mean number of 0.46 errors (*SD* = 0.84) on the SDMT (without distractors) and a mean number of 0.48 errors (*SD* = 0.86) on the SDMT (with distractors). A similar pattern was found in the intact RRMS group, which had a mean number of 0.68 errors (*SD* = 0.96) on the SDMT with and without distractors. This group had a mean number of 0.43 errors (*SD* = 0.85). Therefore, both groups registered a mean of fewer than one error per participant. The impaired RRMS group had a greater number of errors with a mean number of 1.46 errors (*SD* = 1.73) on the SDMT without distractors, and when the distractor was added to SDMT, this group had a mean number of 1.46 errors (*SD* = 1.37).

Table 6.16

Mean and Standard Deviations for Number of Errors (in counts) on the SDMT for each Group and Condition (n =129)

Group	SDMT	*n*	Mean	*SD*	Minimum	Maximum
Healthy Control	Without distractors	50	0.46	0.84	0	4
	With Distractors	50	0.48	0.86	0	4
Intact RRMS	Without Distractors	51	0.68	0.96	0	4
	With Distractor	51	0.43	0.85	0	3
Impaired RRMS	Without distractors	28	1.46	1.73	0	6
	With distractors	28	1.46	1.37	0	5

Poisson regression analysis of the errors on the SDMT with and without distractors

The interaction between group and task was also included in the model. The output indicated that this interaction was not statistically significant, Wald χ^2 (2) = 2.35, p = .309 (see

Table 6.17). This means that the three groups did not have a statistically different rate of errors over the two tasks, namely the SDMT (with and without distractors).

Table 6.17

Poisson Regression Model Statistics using the Number of Errors on the SDMT as a Dependent Variable

	Model Statistics		
	df	Wald χ^2	*p*
Main effects/factors			
Group	2	6.69	.035*
Task	1	0.02	.895
Group * Task	2	2.35	.309
Covariates			
Counterbalance	1	0.61	.433
Age	1	0.28	.598
Gender	1	0.52	.470
Employment	1	0.80	.371
Education	1	0.94	.331
HADS Anxiety Score	1	0.71	.400
HADS Depression Score	1	0.14	.706
WTAR Score	1	1.85	.174

* $p < .05$
Key: WTAR – Wechsler Test of Adult Reading; HADS – Hospital Anxiety and Depression Scale

As the interaction between group and task was revealed not to be significant in the previous model, it did not serve any purpose in the model and added extra 'noise'. This interaction was removed and a new model was run to more clearly see how the predictors were related to the outcome of the number of errors on the SDMT (Table 6.18).

The factor in the model without the group/task interaction was not significant, Wald χ^2 (1) = 0.50, p = .48 (see Table 6.18). This indicated that there was no significant difference in the number of errors made on the SDMT (without distractors) as compared to those on the SDMT (with distractors) for each group.

Table 6.18

Poisson Regression Model Statistics using the Number of Errors in the SDMT as a Dependent Variable after Removing the Interaction Term 'Group/Task' from the Previous Model

	Model Statistics		
	df	Wald χ^2	*p*
Main Effects/Factors			
Group	2	5.81	.055
Task	1	0.50	.479
Covariates			
Counterbalance	1	0.60	.438
Age	1	0.28	.595
Gender	1	0.52	.473
Employment	1	0.79	.374
Education	1	0.95	.330
HADS Anxiety Score	1	0.71	.400
HADS Depression Score	1	0.15	.703
WTAR Score	1	1.86	.172

Key: WTAR – Wechsler Test of Adult Reading; HADS – Hospital Anxiety and Depression Scale

This model also shows that only 'group' was approaching statistical significance, Wald χ^2 (2) = 5.81, p = .055. This result can be understood by the fact that the impaired RRMS group had significantly more errors than the healthy control group (incidence rate ratio (IRR) = 2.36, 95% CI = 1.18-4.73) and the intact RRMS group (IRR=2.34, 95% CI = 1.29-4.29), as reported in Table 6.19. The incidence rate ratio was obtained by exponentiating the Poisson regression coefficient (B) as seen in Table 6.19. The incidence rate ratio of 2.36 and 2.34 indicated that the impaired RRMS had a 2.36- and 2.24-times higher incidence of errors than the healthy control group and the intact RRMS group, respectively. This was regardless of tasks, with or without distractors.

The impaired RRMS group also had significantly more errors than the intact RRMS group (incidence rate ratio (IRR) = 2.63, 95% CI = 1.45-4.78). The incidence rate ratio of 2.63

indicated that the impaired RRMS group had a 2.63 times higher incidence of error than the intact RRMS group when completing both tasks. The difference in the number of errors in the SDMT between the healthy control group and the intact RRMS was not statistically significant, (incidence rate ratio (IRR) = 0.98, 95% CI = 0.47-2.01). The same set of eight covariates used in the previous repeated measures RANCOVA models were also used in the Poisson regression model. No covariate in the model was found to be statistically significant.

Table 6.19

Pairwise Comparison between Groups on Number of Errors made on the SDMT

	Mean Difference	Mean Difference 95% CI		B	*SE*	95% Wald CI		Wald χ^2	*p*
Intact RRMS vs HC	1.01	0.50	2.03	0.01	0.36	-0.69	0.71	0.00	.98
IRR (Intact RRMS vs HC)				1.01	0.36	0.50	2.03		
Impaired RRMS vs HC	2.36	1.18	4.73	0.86	0.35	0.17	1.55	5.88	.015*
IRR (Impaired RRMS vs HC)				2.36	0.84	1.18	4.73		
Impaired RRMS vs Intact RRMS	2.34	1.29	4.25	0.85	0.30	0.25	1.45	7.80	.005**
IRR (Impaired RRMS vs Intact RRMS)				2.34	0.71	1.29	4.25		

*$p < .05$
** $p < .01$
IRR=incidence rate ratio

Poisson regression analysis of the errors on the Stroop without and with distractors

Table 6.20 shows the means and standard deviations, as well as the ranges of the number of errors revealed on the Stroop by group and task. The healthy control group had a mean number of 0.28 (*SD* = 0.78) errors on the Stroop (without distractors) and a mean number

of 0.24 (*SD* = 0.69) errors on the Stroop (with distractors). For the intact RRMS group, the mean number of errors on the Stroop (without distractors) was 0.29 (*SD* = 1.10) and the mean number of errors on the Stroop (with distractors) was 0.12 (*SD* = 0.43). The impaired RRMS group had a mean number of 1.07 errors (*SD* = 2.16) on the Stroop (without distractors) and when distractors were added to the Stroop, the impaired RRMS had a mean number of 1.29 errors. Interestingly, both the healthy control and the cognitively intact RRMS groups had fewer errors on the Stroop with distractors compared to the impaired group which had a greater number of errors on the Stroop with distractors.

Table 6.20

Means and Standard Deviations for the Number of Errors in Counts on the Stroop for each Group and Condition (n =129)

Group	Stroop	*n*	Mean	*SD*	Minimum	Maximum
Healthy Control	Without distractors	50	0.28	0.78	0	3
	With distractors	50	0.24	0.69	0	4
Intact RRMS	Without distractors	51	0.29	1.1	0	6
	With distractors	51	0.12	0.43	0	2
Impaired RRMS	Without distractors	28	1.07	2.16	0	9
	With distractors	28	1.29	2.11	0	7

A Poisson regression model was run with the dependent variable being the number of errors on the Stroop and the two factors in the model being group and task. The interaction between group and task as well as the list of eight covariates included in the previous model were also included. This was to determine whether there were any significant differences in the number of errors made between the groups on each version of the Stroop.

In the model (see Table 6.21), the interaction between group and task was not significant (Wald χ^2 (1) = 1.14, p = .29). This means that the three groups did not have a statistically different rate of errors between the two tasks, the Stroop (without and with distractors). As this interaction term was found to be non-significant, it did not serve any purpose in the model and was therefore removed. The model was rerun, to clarify how the predictors were related to the dependent variable, the number of errors on the Stroop.

Table 6.21

Poisson Regression Model Statistics using the Number of Errors in the Stroop as Dependent Variable

	Model Statistics		
	df	Wald χ^2	*p*
Main effects/factors			
Group	2	12.18	<.001***
Task	1	0.11	.737
Group * Task	2	1.14	.286
Covariates			
Counterbalance	1	0.12	.724
Age	1	3.6	.058
Gender	1	0.15	.702
Employment	1	0.48	.489
Education	1	0.07	.785
HADS Anxiety Score	1	0.51	.475
HADS Depression Score	1	9.61	.002**
WTAR Score	1	5.62	.018*

*p < .05
** p < .01
*** p < .001
Key: WTAR – Wechsler Test of Adult Reading; HADS – Hospital Anxiety and Depression Scale

The statistics of the re-run model (Table 6.22) suggested that the 'task' factor was not significant (Wald χ^2 (1) = 1.66, p = .20). Another factor 'group' was statistically significant (Wald χ2 (1) = 12.25, p < .001), such that the intact RRMS group had a model adjusted 0.17 times lower incidence of error than the healthy control group, (IRR) = 0.17, 95% CI = 0.06-0.45).

Table 6.22

Poisson Regression Model Statistics using Number of Errors in the Stroop as Dependent Variable after Removing Interaction Term 'Group/Task' from the Previous Model

	Model Statistics		
	df	Wald χ^2	*p*
Main effects/factors			
Group	2	12.25	<.001***
Task	1	1.66	.197
Covariates			
Counterbalance	1	0.12	.724
Age	1	3.6	.058
Gender	1	0.15	.702
Employment	1	0.48	.489
Education	1	0.07	.785
HADS Anxiety Score	1	0.51	.475
HADS Depression Score	1	9.61	.002**
WTAR Score	1	5.62	.018*

*$p < .05$
** $p < .01$
*** $p < .001$
Key: WTAR – Wechsler Test of Adult Reading; HADS – Hospital Anxiety and Depressions Scale
Regarding the covariates in the model (Table 5-23), the HADS depression score was significant as was the WTAR score. This revealed the effects of depression on cognitive performance, while the WTAR score mitigated against errors. The rest of the six covariates in the model were all found to have a non-significant relationship to the number of errors on the Stroop.

Regarding the covariates in the model (Table 6.23), the HADS depression score was significant as was the WTAR score. This revealed the effects of depression on cognitive performance, while the WTAR score mitigated against errors. The rest of the six covariates in the model were all found to have a non-significant relationship to the number of errors on the Stroop.

Table 6.23

Pairwise Comparison of Three Groups

	Mean Difference	Mean Difference 95% CI		B	SE	95% Wald CI		Wald χ^2	*p*
Intact RRMS vs HC	0.17	0.06	0.45	-1.79	0.51	-2.80	-0.79	12.25	<.001***
IRR(Intact RRMS vs HC)				0.17	0.09	0.06	0.45		
HADS Depression	1.27	1.09	1.48	0.24	0.08	0.09	0.40	9.61	0.002**
IRR(HADS Depression)				1.27	0.10	1.09	1.48		
WTAR	0.91	0.84	0.98	-0.09	0.04	-0.17	-0.02	5.62	0.018*
IRR(WTAR)				0.91	0.04	0.84	0.98		

*$p < .05$
** $p < .01$
*** $p < .001$
Key: IRR=incidence rate ratio; HADS- Hospital Anxiety and Depression Scale; WTAR – Wechsler Test of Adult Reading

Group Comparison Between Healthy Controls and Cognitively Intact RRMS Groups as Defined by Criterion 2

Demographic comparisons between 50 healthy control participants and 51 cognitively intact RRMS participants and their mean scores on the cognitive tests are displayed in Table 6.24. There were no statistically significant differences between the healthy control and RRMS groups on age, gender or highest level of education. The control group had 10 unemployed participants, which represented 20% of the sample compared to 20 unemployed participants in the intact RRMS group representing 39.2% of the sample. Although cognitively intact RRMS patients are by definition considered as cognitively functional, a significantly higher proportion of this intact RRMS sample was unemployed as compared to the control group.

Table 6.24

Healthy Control and Intact RRMS (using Criterion 2) Between-Group Statistics on Demographic Characteristics, MACFIMS, the SDMT with Distractors, and the Stroop with and without Distractors (n = 101)

	Group			
	Healthy Control *n* = 50	Intact RRMS *n* = 51		
Characteristics	Mean (*SD*)	Mean (*SD*)	*t*-test/χ^2	*p*
Age, years	41.46(10.2)	40.71(9.34)	0.387	.699
Female sex — n(%)	34(68%)	37 (72.5%)	$\chi2 = 0.260$	.617
Education, years	15.52(1.31)	15.80(2.19)	-0.750	.455
Employment — n(%)				
Employed	40(80%)	31(60.8%)	$\chi2 = 4.465$	.035*
Unemployed	10(20%)	20 (39.2%)		
Duration of RRMS, years	-	10.50 (6.04)	-	-
EDSS score	-	1.63 (1.16)	-	-
WTAR score	36.51(5.92)	38.27 (4.42)	-1.640	.105
HADS score				
Anxiety	4.22(3.14)	10.75 (4.18)	-8.870	<.001***
Depression	2.44(2.43)	7.10 (3.51)	-7.761	<.001***
Total	6.66(4.95)	17.84 (6.77)	-9.490	<.001***
MACFIMS				
PASAT – 3 seconds	46.46(9.66)	46.96 (8.97)	-0.270	.788
PASAT – 2 seconds	37.33(8.99)	34.16 (7.67)	1.857	.067
CVLT-II-total	54.96(9.96)	54.16(8.77)	0.430	.668
CVLT-II –delayed recall	12.06(2.74)	12.14(3.08)	-0.133	.894
BVMT-R – total recall	22.14(6.14)	23.86(5.90)	-1.437	.154
BVMT-R – delayed recall	9.14(2.05)	9.31 (1.88)	-0.444	.658
D-KEFS – Sorting	8.96(2.47)	9.90 (2.03)	-2.097	.039*
D-KEFS – Description	31.83(9.16)	35.27 (8.00)	-2.019	.046*
COWAT	43.08(11.0)	42.44 (14.04)	0.253	.801
JLO	23.50(4.66)	24.43(4.20)	-1.055	.294
SDMT without distractors	12.32 (1.72)	13.25(2.39)	-2.236	.028*
Other Cognitive Tests				
SDMT with distractors	13.12(1.80)	14.04(2.76)	-1.983	.050*
Stroop without distractors	22.38(5.70)	24.34(7.33)	-1.496	.138
Stroop with distractors	23.88(6.74)	26.66(8.26)	-1.853	.067
Errors on SDMT and Stroop				
Errors on SDMT no distractor	Mean Rank=46.84	Mean Rank = 54.16	z = 1.456	.145
Errors on SDMT with distractor	Mean Rank=52.35	Mean Rank = 49.68	z = -0.577	.564
Errors on Stroop no distractor	Mean Rank=52.39	Mean Rank =49.64	z = -0.873	.383
Errors on Stroop with distractor	Mean Rank=53.02	Mean Rank =49.02	z = -1.222	.222

*$p < .05$
** $p < .01$
*** $p < .001$
Key: WTAR – Wechsler Test of Adult Reading; HADS – Hospital Anxiety and Depression Scale; EDSS – Expanded Disability Status Scale; PASAT – Paced Auditory Serial Addition Test; CVLT-II – California Verbal Learning Test, second edition; BVMT-R – Brief Visuospatial Memory Test- Revised; D-KEFS – Delis-Kaplan Executive Function System; COWAT – Controlled Oral Word Association Test; JLO – Judgement of Line Orientation Test; SDMT – Symbol Digit Modalities Test

There was no difference between the control group and intact RRMS group on the WTAR score. However, the HADS anxiety, HADS depression and HADS total scores were all significantly greater in the intact RRMS group compared to the control group, signifying that the later were more impacted by mental health symptoms.

Of the MACFIMS tests, statistically significant differences were found between the healthy controls and cognitively intact RRMS groups on the D-KEFS sorting and description tests, and on the SDMT (with and without distractors). As can be seen in Table 6.24 the cognitively intact RRMS group had significantly higher scores on both tests, revealing a cognitively able group. On the SDMT (without distractors) the mean processing speed of the healthy control group was 12.32 seconds (*SD* =1.72 seconds), as compared to the mean processing speed of 13.25 seconds (*SD* = 2.39 seconds) of the intact RRMS group, which was statistically significant, t(99) = -2.236, p = .028. Even though the cognitively intact RRMS group was not statistically different on most tests on the MACFIMS and in fact superior on the DKEFS sorting and description, compared to the healthy control group, the SDMT (with and without distractors) revealed the subtle cognitive impairment of the intact RRMS group.

When auditory distractors were added to the SDMT, the mean processing speed for the healthy control group and the intact RRMS group was 13.12 seconds (*SD* = 1.80 seconds) and 14.04 seconds (*SD* = 2.76 seconds), respectively. The results of an independent samples *t*-test revealed that the intact RRMS group took statistically longer time to complete the SDMT with distractors than the control group. This is an important difference central to the research question of this study and will be discussed in detail in the next chapter. No statistically significant differences were shown between the healthy control and the intact RRMS groups on the processing time of both the Stroop tests (with and without distractors) although the latter had a trend towards significance.

Figure 6.40 is a graphic representation of impairment in percentages of the healthy control (pink) and cognitively intact RRMS (green) groups. The strong cognitive performance of the intact RRMS group can be clearly seen as well as that of the control group on the SDMT (with distractors) and the Stroop (with and without distractors)

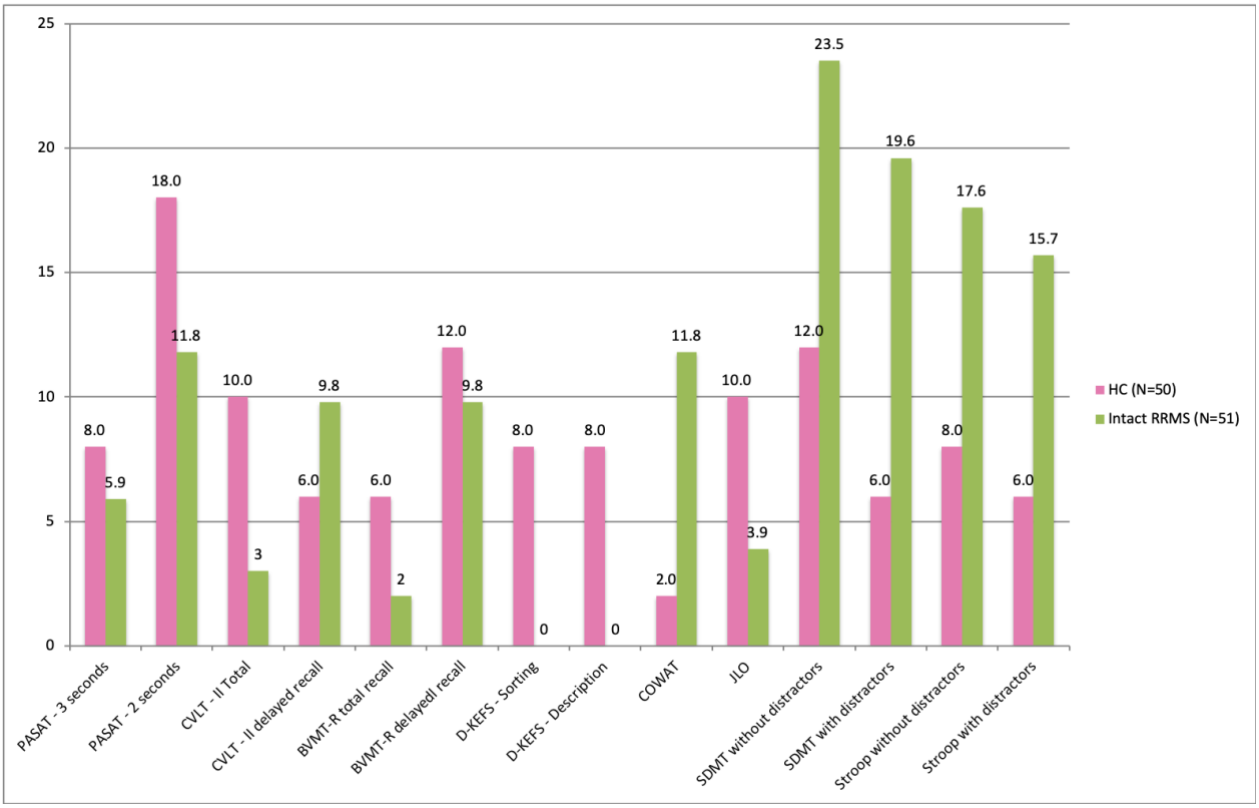


Figure 6.40

Impairment Rate in Percentages of the Healthy Controls (n = 50) and RRMS (n = 79) on the MACFIMS tests, the SDMT (with distractors) and the Stroop (with and without distractors)

A Mann-Whitney U test was run to evaluate possible differences in the numbers of errors made on the SDMT without distractors between the healthy control group and the intact RRMS group. The distributions of the number of errors were similar for both groups, as assessed by visual inspection (see Figure 6.41). There was no statistically significant difference

in the number of errors on the SDMT made by the healthy control group (mean rank = 46.84) and the intact RRMS group (mean rank = 54.16), U = 1067, z = 1.456, p = .145, using an exact sampling distribution for U (Dineen & Blakesley, 1973).

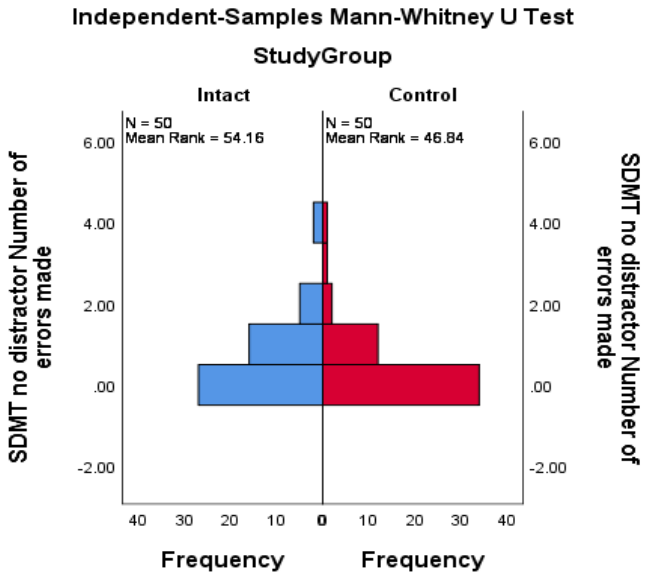


Figure 6.41

Histogram of number of errors on the SDMT without distractors for the two groups, healthy controls versus intact RRMS

A Mann-Whitney U tests was similarly computed to test possible differences in the numbers of errors between the two groups when auditory distractors were added to the SDMT. The results suggested no statistically significant difference in the number of errors on the SDMT (with distractors) were made by the control group and the intact RRMS group (see Figure 6.42).

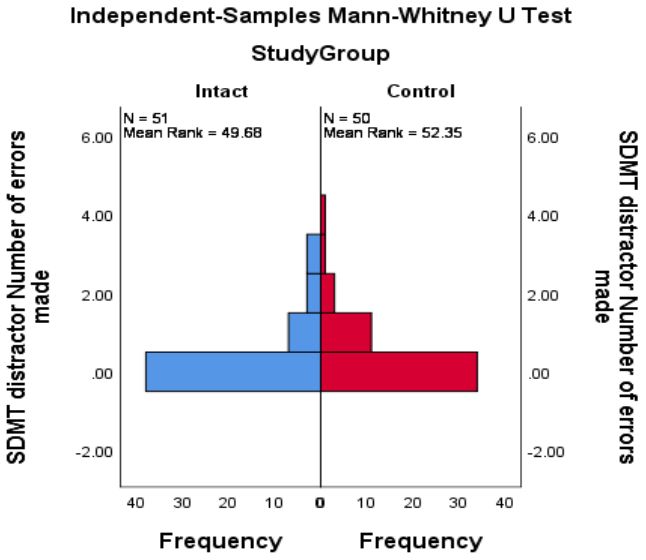


Figure 6.42

Histogram of Number of Errors on the SDMT with Distractors for the Two Groups, Healthy Controls and Intact RRMS

Further Mann-Whitney U tests were run to estimate if there were differences in the numbers of errors made on the Stroop (without distractors) and the Stroop (with distractors) between the healthy control group and the intact RRMS group. Distributions of the error numbers for both groups were similar, as assessed by visual inspection (see Figure 6.43 and Figure 6.44).

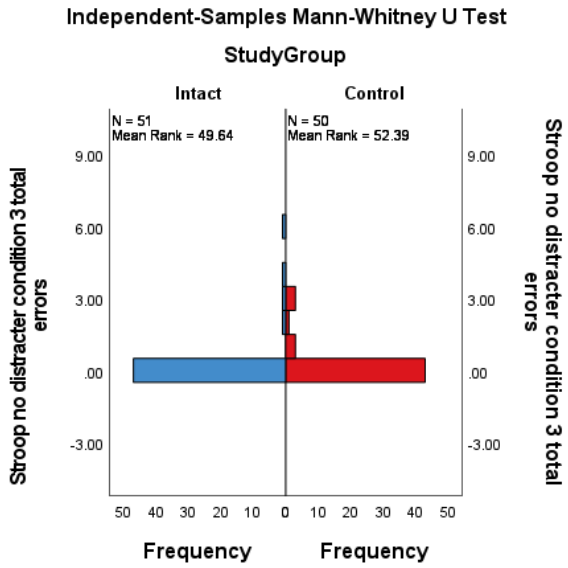


Figure 6.43

Histogram of Number of Errors on the Stroop (without distractors) for the Two Groups, Healthy Controls and Intact RRMS

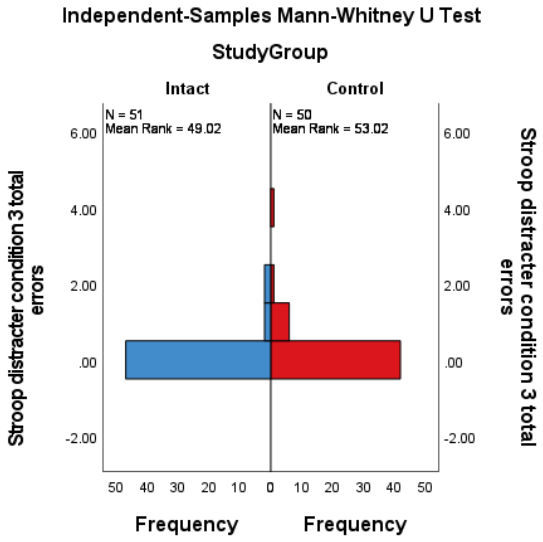


Figure 6.44

Histogram of Number of Errors on the Stroop (with distractors) for the Two Groups, Healthy Controls and Intact RRMS

To summarize, on the demographic and disease-related variables, statistically significant differences were found in employment status, and the three HADS scores (Anxiety, Depression and Total). The cognitively intact RRMS group had a significantly higher proportion of unemployed participants, with significantly higher mean HADS scores, as compared to the control group. Among the cognitive tests, statistically significant differences were found on three tests, the D-KEFS (sorting and description) and the SDMT with distractors. The intact RRMS group achieved significantly higher scores in both D-KEFS tests, which assess executive functioning, and there was a trend towards significance on the PASAT – 2 second compared to the healthy controls. There were also no statistically significant differences in the number of errors made on the SDMT (with and without distractors) and the Stroop (with and without distractors) between the two groups. Although the intact RRMS group was clearly well functioning on the majority of the MACFIMS tests compared to the healthy control group significant differences were found on processing speed on the SDMT (with and without distractors). This was a measure of interest which showed that the intact RRMS group took significantly longer to process information than the healthy control group. Interestingly, the time difference within the two groups on the SDMT (without distractors) was 0.93 and on the SDMT (with distractors) was 0.92, which were virtually the same. The following section examines the differences between the two groups using Criterion 1 when the groups were not adjusted for the practice effect of the SDMT as part of the MACFIMS.

Group Comparison Between Healthy Controls and Cognitively Intact RRMS Groups as Defined by Criterion 1

This section discusses the comparisons on demographic data, neurological data and cognitive test results between 50 healthy controls participants and 46 intact RRMS participants using Criterion 1 to determine global impairment, as a contrast with the results obtained when

Table 6.25

Healthy Control and Intact RRMS (as defined by Criterion 1) Between-Group Statistics in Demographic Characteristics, MACFIMS, the SDMT with Distractors, the Stoop with and without Distractors (n = 96)

	Group			
	Healthy Control *n* = 50	Intact RRMS *n* = 46		
Characteristics	Mean (*SD*)	Mean (*SD*)	*t*-test/χ^2	*p*
Age, years	41.46(10.2)	40.72(9.41)	0.370	0.712
Female sex — n(%)	34(68%)	35 (76.08%)	χ^2 = 0.775	0.379
Education, years	15.52(1.31)	15.80(2.19)	-0.764	0.447
Employment — n(%)				
Employed	40(80%)	28 (60.87%)	χ^2 = 4.244	0.039*
Unemployed	10(20%)	18 (39.13%)		
Duration of RRMS, years	-	10.50 (6.04)	-	-
EDSS score	-	1.63 (1.16)	-	-
WTAR score	36.51(5.92)	38.70 (4.26)	-2.040	0.044*
HADS score				
Anxiety	4.22(3.14)	10.48 (4.22)	-8.189	<.001***
Depression	2.44(2.43)	6.93 (3.54)	-7.192	<.001***
Total	6.66(4.95)	17.41 (6.75)	-8.838	<.001***
MACFIMS				
PASAT – 3 seconds	46.46(9.66)	47.83 (8.45)	-0.734	0.464
PASAT – 2 seconds	37.33(8.99)	34.89 (7.54)	1.397	0.166
CVLT-II-total	54.96(9.96)	55.17 (6.95)	-0.123	0.903
CVLT-II –delayed recall	12.06(2.74)	12.57 (2.62)	-0.921	0.360
BVMT-R – total recall	22.14(6.14)	24.30 (5.78)	-1.774	0.079
BVMT-R – delayed recall	9.14(2.05)	9.30 (1.92)	-0.405	0.687
D-KEFS – Sorting	8.96(2.47)	9.96 (2.13)	-2.111	0.037*
D-KEFS – Description	31.83(9.16)	35.52 (8.32)	-2.066	0.042*
COWAT	43.08(11.0)	43.33 (14.20)	-0.096	0.923
JLO	23.50(4.66)	24.70 (3.61)	-1.396	0.166
SDMT no distractor	12.32 (1.72)	12.87 (2.19)	-1.369	0.174
Other Cognitive Tests				
SDMT with distractor	13.12(1.80)	13.53(2.30)	-0.982	0.329
Stroop no distractor	22.38(5.70)	23.51(6.47)	-0.909	0.366
Stroop with distractor	23.88(6.74)	25.58 (7.09)	-1.206	0.231
Errors on SDMT and Stroop				
Errors on SDMT without distractors	Mean Rank=45.25	Mean Rank = 51.06	z = 1.194	0.233
Errors on SDMT with distractors	Mean Rank=50.58	Mean Rank = 46.24	z = -0.979	0.328
Errors on Stroop without distractors	Mean Rank=49.54	Mean Rank =47.37	z = -0.690	0.490
Errors on Stroop with distractors	Mean Rank=50.12	Mean Rank =46.74	z = -1.035	0.301

*$p < .05$;
** $p < .01$
*** $p < .001$
Key: WTAR – Wechsler Test of Adult Reading; HADS – Hospital Anxiety and Depression Scale; EDSS – Expanded Disability Status Scale; PASAT – Paced Auditory Serial Addition Test; CVLT-II – California Verbal Learning Test, second edition; BVMT-R – Brief Visuospatial Memory Test- Revised; D-KEFS – Delis-Kaplan Executive Function System; COWAT – Controlled Oral Word Association Test; JLO – Judgement of Line Orientation Test; SDMT – Symbol Digit Modalities Test

Criterion 2 was used. The results of the statistical tests between the two groups were similar when Criterion 1 and 2 were used, except on the two versions of SDMT (without and with distractors). In the previous table (6.24), the 51 cognitively intact RRMS participants took a significantly longer time to complete the SDMT without distractors, as well as the SDMT with distractors (p = .028 and p = .050, respectively) as compared to the healthy control group. However, when using global impairment Criterion 1 to separate intact participants (n = 46) from impaired subjects (n = 33) within the RRMS group, the statistically significant differences in the processing speed of the two versions of the SDMTs (without and with distractors) were not found between the 50 healthy control participants and the 46 cognitively intact RRMS participants (SDMT without distractors: $t(94) = -1.369$, $p = 0.174$; SDMT with distractor: $t(94) = -0.982$, $p = .329$). This result appears to substantiate the confounding influence of the SDMT inclusion in both the MACFIMS and as a dependent variable, and suggest that its exclusion was warranted when determining global impairment.

Conclusion

The principal focus of this research was to determine the cognitive performance of the intact RRMS participants in comparison to the healthy control group. When the SDMT was excluded from the MACFIMS in the case of Criterion 2 significant differences were revealed on both versions of the SDMT between the healthy control and cognitively intact RRMS groups, as the performance of the latter group was significantly impaired compared to the former group. This was the result despite the fact that the cognitively intact RRMS group was cognitively stronger than the control group. These results addressed the between group hypotheses and answered the primary research question. A difference between the healthy control and cognitively intact participants was not observed in the Stroop results, nor in the number of errors made on both versions of the SDMT and the Stroop.

The second set of hypotheses involved within group comparisons of the cognitively intact RRMS and cognitively impaired RRMS participants. Both groups performed significantly poorer on the SDMT and Stroop with distractors compared to the both these tests without distractors.

In the next chapter the results will be more fully explored and considered in relation to the primary research question and hypotheses. Auditory distraction theory will also be discussed and connections made to the outcomes of the present research.

CHAPTER 7

DISCUSSION

Introduction

Distraction, mostly affecting the auditory and visual modalities, is ubiquitous and unavoidable in daily life. People with MS have a propensity to distractibility which impacts speed of information processing. This is the cognitive domain most often affected in MS and underlies additional vital cognitive domains such as attention and working memory (McNicholas et al., 2018; Patel et al., 2017). Yet little research has been undertaken in the MS population on the unique role distraction has in impacting information processing speed. To fill the gap in research, the central aim of the current research was to explore the effect of auditory distraction on information processing speed in RRMS. Specifically, on people with RRMS who test as cognitively intact on the MACFIMS, yet often experience cognitive difficulties in real-world settings. In this study, the distraction took the form of embedded unintelligible speech in two of the most commonly used cognitive tests with people experiencing MS namely, the SDMT and the Stroop test. These are targeted tests of information processing speed and the introduction of auditory distractors in both tests requires inhibitory control of the embedded unintelligible speech to maintain focused attention (Randolph et al., 2017). The tests were engineered to mimic real-world distractions to provide greater ecological validity, since the majority of cognitive assessments in the MS population are conducted in controlled laboratory settings, which may not accurately reflect the

cognitive demands encountered in daily life. Both tests were presented in computerized form so that administration formats were not confounding factors.

The use of embedded distractors was hypothesized to increase the sensitivity of these tests in detecting impairments in information processing speed in people with RRMS who test as cognitively intact on the MACFIMS compared to a healthy control group. Results from the current study revealed the added sensitivity of both versions of the SDMT in exposing deficits in information processing speed in the cognitively intact RRMS group. Additionally, it was hypothesized that the distractors embedded in the SDMT and the Stroop would result in longer processing speed when compared to performance on the two tests without distractors in both the cognitively intact and cognitively impaired RRMS groups. Results did indeed reveal significantly slower information processing speed in both these groups in the SDMT with distractors and the Stroop with distractors compared with the non-distractor versions, highlighting the increased sensitivity of the two tests with distractors. The importance of these findings is that the two tests (with and without distractors) can be used separately or in conjunction as sensitive cognitive screening devices. They can be routinely, quickly and easily administered by any clinical professional to track cognitive status at initial diagnosis and monitor cognitive status at follow-up neurological assessments.

The statistical analyses in the current study revealed certain significant results and trends pertinent to the research aims and the subsequent sections discuss the most important results in further detail. Firstly, the discussion includes an examination of the demographic differences between the healthy control and total RRMS groups and extent of impairment on the MACFIMS. Secondly, impairments found on this test battery resulted in the separation of the RRMS group

into the cognitively intact and impaired groups. The disparities between these two groups is then explored. Thirdly, the differences between the healthy control and the intact RRMS groups is considered. The research aims and hypotheses will be discussed in the light of the results of the analyses. These are then explored in the context of relevant literature and research that was reviewed at the onset of this thesis.

Overview of Main Findings

The RRMS group in this study had a global cognitive impairment rate of 41.77% according to failure of three out of 11 indices on the MACFIMS. This rate of cognitive impairment in people with RRMS is consistent with the literature, which gives ranges between 34.8 to 51.1% (Migliore et al., 2017; Papathanasious et al., 2014). There are at least three possible reasons for the large disparity in these rates of cognitive impairment. First, is the level of disability of participants. There is a large span of EDSS scores for people with RRMS, ranging from 0 to > 6.5 (Kurtzke, 1983). This was reflected in certain studies, as mean disability scores were higher than that of the present study, which was, EDSS = 2.04 (Denney et al., 2005; Ruano et al., 2017). Second, a variety of different neuropsychological tests tend to be used in the assessment process with some batteries more comprehensive than others (Migliore et al., 2017). A third reason may be that cut off scores for the MACFIMS differed across studies. Some used two out of the 11 indices to indicate failure on the test, which resulted in a larger number of people designated with global impairment (Benedict, Cookfair et al., 2006; Lapshin et al., 2011). However, there is a trend in recent years to designate global impairment as three out of 11 indices. The reason for this shift is that if a study participant fails one version of a test, such as the PASAT-3, it is likely that the following iteration

(the PASAT-2) will be failed (Migliore et al., 2017; Patel et al, 2017). Failure of three tests thus covers at least two of the seven cognitive domains that are evaluated in the MACFIMS battery.

Total Relapsing Remitting Multiple Sclerosis and Healthy Control Groups

All participants, people with RRMS and healthy controls met the same inclusion and exclusion criteria outlined in the Methods Chapter and visual acuity was verified. There was a close statistical matching of the healthy control group to the RRMS group by age, ratio of female to male, years of education and premorbid IQ based on the Wechsler Test of Adult Reading (WTAR) scores. This data (excluding disease duration and EDSS) was used to compare the two groups as differences in these covariates could influence the SDMT (with and without distractors) and the Stroop (with and without distractors). It is an essential tenet when assessing cognition in MS consider interference by possible confounders (Goretti et al., 2014). Results of the comparisons revealed that the number of people who were unemployed in the RRMS group was significantly greater than that of the healthy control group, and the same held true for mental health status in the three scores of the HADS (anxiety, depression and total score). The healthy control group obtained significantly better scores on nine out of the 14 cognitive tests with the largest differences in the SDMT (with and without distractors) and the Stroop (with and without distractors). This highlighted the discriminant strength of these two tests in revealing cognitive impairment in people with RRMS. Crucially, the greatest rate of percentage difference ($p < .001$) between the two groups on all tests was on the SDMT with distractors. It is a noteworthy result, reinforcing the importance of the SDMT with distractors as a highly sensitive cognitive screening and monitoring tool (Drake et al., 2010; Healy et al., 2021; Lopez-Gongora et al., 2015; Silva et al., 2019; Strober et al., 2019; van Schependom et al., 2014).

The differences between the groups in employment status, anxiety and depression will be explored in the following sections. Level of education will be also discussed as it was the only covariate found to influence the results when the SDMT without distractors was compared to the SDMT with distractors. This will be followed by a discussion of differences highlighted between the groups on the cognitive tests.

Employment

Unemployment rates are known to be high early in the MS disease course with 43% of people with MS leaving the workforce within the first three years of diagnosis (Strober, 2020). In the present study despite matched demographic variables, significantly more people with RRMS were unemployed compared to the healthy controls at a ratio of 2.4 to 1. The rate of unemployment of 44% in the present MS groups is compatible with the literature figures of 50% for people with mild RRMS (Clemens & Langdon, 2018). In the present study the RRMS group had minimal to mild physical disability with a mean EDSS score of 2.04 out of a maximum of 10. This level of mild disability would not normally preclude employment, as mobility and dexterity are largely intact. This high rate of unemployment is concerning as it impacts economic status, ability to utilize cognitive capacity, self-esteem and quality of life (Strober et al., 2020). An explanation for this elevated level of unemployment is cognitive impairment, especially in information processing speed and memory, which is widely seen as a mediating factor in job loss in MS and contributes more to attrition from work than physical disabilities (Bøe Lunde et al., 2014; Macaron et al., 2020; Morrow et al., 2010; Strober et al., 2014). Cognitive impairment also often leads to changes in work status resulting in less prestigious positions (Morse et al., 2013; Strober et al., 2014; van Gorp et al., 2019).

In the present research a number of cognitive tests revealed significant differences between the healthy control and RRMS groups. The healthy control group performed significantly better on the CVLT-11 total and delayed recall, the BVMT-R delayed recall. There was also significant difference found on the PASAT – 2 with lower significance on the PASAT – 3. These results are consistent with a large meta-analytic study that differentiated rates of reduced work hours and unemployment in MS groups from control groups by means of the SDMT, the PASAT 2 and 3, the BVMT-R and CVLT-11, reflecting significant difficulties with speed of information processing, deficits in memory with immediate and delayed recall, and in visual and verbal modalities (Clemens & Langdon, 2018). Thus, the argument that cognitive impairment is a major contributor to unemployment in RRMS remains a likely explanation in the present research, particularly as years of education and WTAR scores were matched. It is worth noting that the highest significant differences between the groups were revealed on both versions of the SDMT and both versions of the Stroop. The SDMT is frequently referred to in the literature as the most effective test at linking cognitive ability to work challenges and employment status (Benedict et al., 2016; Strober et al., 2014). Thus, poorer performance on this test is a predictor of unemployment and general cognitive competence (Campbell et al., 2017; Macaron et al., 2020).

Despite the differences in employment status between the healthy controls and the RRMS groups, it did not emerge as a significant covariate in the analysis.

Anxiety and Depression

The RRMS group was significantly more impacted by anxiety and depression than the healthy control group. Affective symptoms are apparent at an early stage of MS even before a definitive diagnosis and are considerably higher than the general population (Filser et al., 2022).

Data from published reports of lifetime prevalence of depression in people with MS vary according to methodological approach from 25% to 50% which is nearly three times the lifetime prevalence for the general population. The lifetime prevalence of anxiety disorders is 45%, double that of the general population (Feinstein, 2007).

Differences in the present study were detected on the HADS scores (anxiety, depression and total) and the RRMS group obtained significantly higher scores on all three variables compared to the healthy control group. Comorbidity of depression and anxiety in MS is common and the HADS total of 22% in this study is compatible with comorbid scores for depression and anxiety of approximately 20.1% for people with MS (Leavitt et al., 2020). It is important however, to break down anxiety and depression into separate categories, to understand these differences, whether and to what extent they may influence impairment in cognition in MS. In the general Canadian working-age adult population the prevalence of a depressive disorder is 5.4% to 9.8% and the prevalence of an anxiety disorder is 4.6% to 10.8% (Dobson et al., 2020). The present study was conducted with Canadian participants and the healthy controls obtained a depression rate of 4.88%, marginally lower than the general Canadian range and an anxiety rate of 8.44%, which is within the range of the Canadian numbers. Therefore, the anxiety and depression scores of the healthy control group were representative of the general working population. However, the RRMS group presented with three times the rate of depression (7.45 to 2.44) and two-and-a-half times the rate of anxiety (10.17 to 4.22) compared to the healthy control group. This result is in accordance with previous studies, which found that major depression occurred in people with MS at three times the rate reported in the community at large (Diamond et al., 2008; Feinstein, 2007; Ribbons et al., 2017). Yet the rates of depression in the present study of 9.43% and anxiety of

13%[21], are lower than the summative prevalence found in two meta-analytic studies. These studies presented disparate numbers; the first study measured the rate of depression at 21% and anxiety at 39%, while the second study reported depression with a pooled mean prevalence of 30.5% and 22.1% for anxiety (Boeschoten et al., 2016; Marrie et al., 2015; Marrie et al., 2018). Other studies give a range of 15% to 22% for depression and 9% to 15% for anxiety (Filser et al., 2022; Leavitt et al., 2020). The reason for heterogeneity in these metanalytic studies is difficult to establish. It may be due to different cutoff scores used for the HADS. The cutoff score of 8 and above for both subscales is most often used however, some cut off scores are lower at 7 or at higher at 10 (Boeschoten et al., 2016). The HADS has been validated for the Canadian MS population using a cutoff score of 8 and above with a high sensitivity of 90% and specificity of 87.3% for the depression subscale and sensitivity of 88.5% and specificity of 80.7% for the anxiety subscale (Honarmand & Feinstein, 2009). Hence the cutoff score of 8 or above was utilized in the present study. A further reason for heterogeneity in prevalence rates may be that many studies do not separate out the different disease courses when conducting analyses on depression and anxiety. It is probable that individuals with less disease burden and disability will exhibit fewer mental health symptoms (Jones et al., 2012; Marrie et al., 2021). A meta-analytic study that extracted mental health data from different MS subtypes showed that the most commonly used scale was the HADS and the overall prevalence of depression in people with RRMS was 15.8% and 21.4% for anxiety. These numbers are lower than the prevalence rates for depression and anxiety given by the cited studies that do not separate the different disease courses (Feinstein, 2011; Marrie et al., 2021; Nunnari et al., 2015; Patel et al., 2019). EDSS numbers were not available for all 12 studies, but

[21] Prevalence rate at time of testing and not lifetime prevalence rate.

were greater than those in the present study (Peres et al., 2022). However, rates of depression (9.43%) anxiety (13%) from the present study are still lower than the meta-analysis numbers. The reason may be that the sample from the current study was drawn solely from a RRMS cohort with a mean EDSS score of 2.04, which is regarded as a low score reflected minimal disability (Kurtzke, 1983). Thus, the low level of disease load is consistent with the lower rates of anxiety and depression found in the current study (Feinstein et al., 2014)

Anxiety and depression are prevalent in MS and are identified in numerous studies as affecting cognition. Areas in the brain that contain both atrophy and white matter focal lesion load, deemed to be involved in mood disorders and emotional dysregulation, overlap with essential regions that are also related to cognitive impairment in MS (Portaccio, 2016). Thus, in the present study there was a concern that anxiety and depression were potential confounding variables when evaluating the differences in speed of information processing in the distractor SDMT and the distractor Stroop. Depression was related to difficulties in learning, executive functioning and impaired information processing speed and was also associated with lower word fluency and poorer recall of visual-spatial information (Diamond et al., 2008; Diamond, 2013; Feinstein, 2006; Patel & Feinstein, 2019). None-the-less, the extent of depressive symptoms impacted cognitive tasks differently as lowered information processing is argued to be only linked to depression if the cognitive demands on a test were high, requiring effortful information processing (Lubrini et al., 2016). Additionally, mild depression and minimal disability did not appear to influence cognition in the areas of information processing speed, verbal and visual memory (Skorve et al., 2020). In the current research the prevalence rates of depression and anxiety were less than those reported in other studies, the disability level of the MS was low and the cognitive load on both the SDMT

and Stroop was low as they are not difficult tests to perform. Given these factors and evidence from the previous studies cited, there was a high probability that depression and anxiety were not confounding covariables that influenced the dependent variables. This was confirmed by statistical analyses.

Importantly neither the variables of employment status nor mental health status were confounding factors in the results obtained on the STMD and Stroop both with distractors.

Years of Education

The only covariant of the eight covariates (counterbalance, age, gender, employment status, level of education, HADS anxiety and HADS depression, WTAR) that was statistically significant for the MS group was the level of education (total of all years of schooling attained) in relation to performance on the SDMT. Educational attainment, which enhances cognitive reserve, is recognized as a protective factor that mitigates cognitive impairment in people with MS achieving over 12 years of education (Rimkus et al., 2018; Santangelo et al., 2019). Additionally, higher educational attainment in people with MS is largely independent of information processing speed (Conway et al., 2022). This seems to be the case in the present study as the healthy control, intact RRMS and impaired MS groups all had approximately similar numbers of years of higher levels of educational attainment at, $M = 15.52$, $M = 15.80$, $M = 15.09$ respectively.

In sum, the significant groups differences found with employment status and mental health scores between the healthy control and RRMS did not influence reperformance on the dependent variables (to be discussed in more detail later). The potentially confounding variable of years level of education was also not sufficient to impact the significant differences between the groups on

the SDMT with and without distractors. Differences on the cognitive tests between the healthy control and RRMS groups will be explored in the following section.

Cognitive Tests

The MACFIMS was selected to discriminate cognitive impairment in the RRMS group compared to the healthy control group. This test battery has high construct validity tapping into the most essential areas of cognition affected in MS such as, speed of information processing, verbal and visual memory, word fluency, executive functions and spatial relations. It also only contains measures for which published norms are available and have been specifically standardized for the MS population. (Benedict, Cookfair et al., 2006). The SDMT which is part of the MACFIMS was included with distractors as was the Stroop, with and without distractors. Thus, the cognitive test battery selected for this study contained the MACFIMS, the SDMT (with distractors) and the Stroop (with and without distractors), totaling 14 subtests.

For the most part the tests distinguished distinct cognitive functions, however, it is to be assumed that aspects of cognitive domains intersect and therefore would be significantly correlated (Benedict et al., 2006; Chiaravalloti & DeLuca, 2008; Gromisch et al., 2016; Gromisch et al., 2018; Migliore et al., 2016; Parmentier et al., 2010). Different tests are specifically included in the MACFIMS to explore seven cognitive domains. As expected the bivariate correlations of the 14 tests revealed minimal to moderate overlap between the different tests in each of the seven cognitive domains. Significant intercorrelations were found between those tests that tapped into similar domains, for example, the PASAT 2 and 3 second tests, the CVLT-11 total and delayed tests and both BVMT-R tests. Importantly for this study, the SDMT with distractors was highly positively correlated with both versions of the Stroop, revealing that they encompass a similar

cognitive domain, namely information processing speed. Of the 14 tests administered the PASAT, SDMT and Stroop are rapid serial tests of information processing and significant intercorrelations between these tests were expected. However, the scoring systems are different as scoring on the SDMT and Stroop includes response time, while the PASAT is scored in terms of correct responses. It follows, therefore, that significant negative correlations were found between the PASAT 2 and 3 and the SDMT and Stroop, since a higher score of more correct answers on the former were related to better performance, whereas a higher score or longer time to complete the latter tests on the later likely indicated impairment.

The MACFIMS was developed to assess the cognitive areas most affected in MS and in the present research population was able to discriminate the RRMS participants from the healthy control group on seven of the 11 indices. The RRMS group exhibited significant deficits on the PASAT-3 and PASAT-2 (working memory, speed of information processing, sustained and divided attention and interference inhibition), the CVLT-11, Total and Delayed Recall (learning and immediate and delayed memory of verbal material), BVMT-R, delayed recall, (visuospatial memory), COWAT (verbal fluency and retrieval of words), the SDMT with and without distractors (information processing speed and scanning visual information) and the Stroop, with and without distractors, (information processing speed and inhibition of interference). However, significant differences were not found on tests that assessed executive functioning (D-KEFS-Sorting, DKEFS-Description) and visuospatial processing (JLO). These findings corroborate existing studies of people with RRMS demonstrating impairments in information processing, memory, attention, verbal learning and verbal memory (Johnen et al., 2017; Ruet, Deloire, Charre-Morin, et al., 2013). An influential and large study (n = 461) revealed that information processing

was the most impaired domain followed by impairment in memory in the form of short-term and long-term verbal recall (Noncentini et al., 2006). Fifty-one percent of participants with RRMS regarded as mildly disabled (EDSS ≤ 2.5), a similar EDSS profile to the present study (Mean EDSS = 2.04), were cognitively impaired on the MACFIMS in information processing speed (the most impaired domain), verbal memory and visual memory (short-term and long-term), attention and verbal fluency. This study also found some executive function deficits, which were not found in the current study. This may be as a result of the RRMS group that presented with a slightly greater mean disability score than was the case in the present study. Even a point 0.5 on an EDSS mean score can reveal significant cognitive differences. An example is the present study, whereby there was a 1.00 point mean difference in EDSS between the cognitively intact and impaired RRMS groups and significant differences were found on all 14 subtests, and also on error scores in the SDMT and the Stroop. In the early stages of MS, explicit memory which involves having to learning and repeat verbal and visual material, and episodic memory which encompasses memory of words and/or conversations are often impacted, and these results have been repeated in the present study in the cognitively impaired group (Borghi et al., 2013; Chiaravalloti & DeLuca, 2008, 2018; Migliore et al., 2017). The replication of results from previous studies adds robustness to the present research and validity to established, research outcomes.

The present research is built on the premise that efficient information processing speed, known to be at the core of many cognitive functions, is compromised by distraction. Difficulty dealing with distraction and the subsequent impairments in information processing may be a reason for the cognitive deficits experienced by people with MS from the initial presentation of RRMS (McNicolas et al., 2018; Migliore et al., 2017. Since information processing speed is the

underlying cognitive function compromised in MS at least one or two rapid serial processing tests assessing this process are included in test batteries (Hughes, Denney et al., 2013). The three rapid serial processing tests most widely used in MS assessments are the SDMT, the Stroop and the PASAT. The BRNB-R, one of the first validated and widely used brief neuropsychological battery includes both the PASAT and SDMT to tap into information processing speed, as does the MACFIMS. The BICAMS as a much briefer battery uses only the SDMT. The present research included all three measures and a discussion of the results of the MS group on these tests can elucidate ongoing debates about which test produces the most robust results. Although the PASAT is viewed as a test of information processing speed, it also it also requires significant working memory and a certain level of mathematical ability for adequate performance (Brochet et al., 2008; Drake et al., 2010; Forn et al., 2008; Hughes, Denney et al., 2013; Lopez-Gongora et al., 2015; Sonder et al., 2013). Therefore, information processing speed is only one aspect of the PASAT which may be confounded by the other cognitive processes required for adequate performance, whereas the SDMT and Stroop are more sensitive tests of information processing speed (Drake et al., 2010; Lopez-Gongora et al., 2015).

The PASAT tests are known to be demanding and effortful, especially the PASAT-2 and a number of participants in the MS population struggle to complete this test (Drake et al., 2010; Matias-Guiu et al., 2018; Sonder et al., 2013). This was the case in the present study. Out of a total of 129 participants, 122 completed the PASAT-3 and only 106 the PASAT-2. However, the entire group of 129 completed both versions of the SDMT and both versions of the Stroop. Completing the PASAT – 2 was more challenging than the other tests even within the healthy control group as nine out of the 50 (18%) participants failed the test. However, this is far lower than the RRMS

group with 28 out of 79 (35%) who did not complete the test. Had the PASAT with embedded distractors been chosen for this study it is unlikely that valid results could have been obtained given the complex nature of the test compared to the SDMT and Stroop, both of which yielded significant differences between the two versions of the tests when distractors were added.

As an interesting aside, the neuropathology tapped by the PASAT and SDMT is different although both tests require speed of information processing. White matter inflammation and degeneration, and grey matter atrophy can be observed early in the MS disease process, all of which play key roles in timely and effective information processing (Batista et al., 2012; Sbardella, 2013; Todea et al., 2020). Impaired performance on the SDMT and the PASAT has been correlated with diverse areas of pathology in the brain. White matter microstructural damage is involved in reduced execution on the SDMT however, atrophy of grey matter areas correlates with reduced PASAT performance in people with RRMS (Riccitelli et al., 2019). Thus, impairment on both tests reveal MS pathology, however the SDMT tends to be easier for MS participants to complete, as evident in the current research. It has become the test of choice in MS research and cognitive diagnosis as it produces well-defined results in speed of information processing (Strober et al., 2019). The most significant difference in impairment between the heathy controls and RRMS groups was on the SDMT with distractors ($p < .001$). This is a crucial result for this study highlighting it as the most sensitive test of cognitive impairment in people with MS. Although marginally less, the next significant difference was on the SDMT without distractors, and the Stroop, with and without distractors, once again revealing the sensitivity of these rapid serial processing tests. Significant group differences were also found on the PASAT – 3 (but not the PASAT-2), CVLT-11 Delayed Recall and the COWAT. These tests emphasize the substantial

impairment that the RRMS group displayed in the cognitive domains of information processing speed, attention, working memory, verbal memory including retrieval from long-term storage, and verbal fluency and inhibition of irrelevant information in service of a target task. Moderate group differences were also found in visuospatial memory (BVMT-R; <.05). Importantly, all of these cognitive impairments corroborate those found in the literature (Amato, Portaccio, Goretti, Zipoli, Hakiki, et al., 2010; Berrigan et al., 2013; Deloire et al., 2011; Eilam-Stock et al., 2021; Johnen et al., 2017; McNicholas et al., 2018; Noncentini et al., 2006; Ruet, Deloire., Charre-Morin, et al., 2013). In people with RRMS who tested as cognitively intact on the MACFIMS deficits were observed in executive control processes in the form of rapid task switching, testing cognitive flexibility (Migliore et al., 2018). However, in the former study results of the D-KEFS sorting test were not provided. Had this been the case it would have been valuable to compare results with the present study as the RRMS groups as a whole had a similarly low disability mean score (EDSS = 2.04).

Cognitively Intact Relapsing Remitting Multiple Sclerosis and Cognitively Impaired Relapsing Remitting Multiple Sclerosis Groups

Based on failure of three out of the 11 MACFIMS indices, 41.77% of RRMS participants (*n* = 33) were classified as impaired in cognitive functioning. The remaining 58.23% of RRMS participants (*n* = 46) were classified as cognitively intact. Numbers for people with global cognitive impairment in RRMS on three or more indices on the MACFIMS range from 34.9%, to 43.9% (Amato et al., 2010; Dong et al., 2022; Migliore et al., 2017; Papathanasious et al., 2014)). The range of numbers may be due a number of methodological reasons or even degree of disability and brain pathology within the RRMS participants. However, the percentages found in the present

study lie within this range are so are consistent with other research evaluating only people with RRMS. The reason for the division of the RRMS group into those who were intact and impaired was to assess whether or not the distractors embedded in the SDMT and the Stroop could further discriminate cognitively intact RRMS participants from the healthy control participants. The aim was to establish further sensitivity of these two tests. Impairment was defined a score falling 1.5 *SD* or more below the mean of the healthy group (Migliore et al., 2018). There were significant differences between the groups namely, between the healthy control group and the entire RRMS group, the healthy control group and the intact RRMS group, and the intact RRMS group and the impaired RRMS group.

In order to illustrate how well each of the MACFIMS tests, the Stroop (with and without distractors) and the SDMT (with distractors) were able to discriminate between participants who were cognitively impaired or intact ROC curve analyses were calculated. The ROC curve analyses demonstrated that the SDMT with distractors was the most sensitive of the 14 tests at discriminating between participants with MS who were cognitively impaired or intact. This indicates as hypothesized, that embedding distractors into this test increased its sensitivity at discriminating the cognitive functioning of these two groups. The tests with the highest discriminant values were the BVMT-R, SDMT, the Stroop and the CVLT-11. Three of these four tests, the SDMT, CVLT-11 and BVRT-R constitute the BICAMS and were chosen as a brief 15-minute battery to reveal cognitive impairment in MS, and results in the current research corroborate the sensitive of these three tests in exposing MS cognitive impairment.

Although a comparison of the cognitively intact and cognitively impaired RRMS groups was not an aim in the present study there are some results that are worth discussing. The

cognitively intact and cognitively impaired RRMS groups were not matched as they were generated according global impairment on the MACFIMS, as mentioned above. Significant group differences were not found on gender or years of education. Employment status and HADS scores yielded no differences, contrary to the significant differences between the healthy control and entire RRMS groups on these variables. However, significant group differences were found in age (the impaired group was 5 years older), duration of MS (which was four years longer in the impaired group), and the cognitively intact group had a significantly greater mean WTAR score than the impaired group. The intact RRMS group was significantly better on all 14 subtests (the MACFIMS, the SDMT with distractors and the Stroop, with and without distractors) with 13 out of 14 at the highly significant level ($p > .001$) and made significantly fewer errors than the impaired RRMS group. The greatest percentage difference between the two groups was on the SDMT with distractors, the Stroop with distractors and the CVLT-11, revealing significant impairment in information processing speed, verbal learning and memory, and attention in the cognitively impaired group. These results were obtained despite the fact that there was only a one-point difference on EDSS scores (1.63 compared to 2.61) between the groups. The impaired group's score of EDSS = 2.61 reflects minimal disability, yet the differences between the cognitively intact and cognitively impaired RRMS groups on the cognitive tests were far more significant and wide-ranging than those between the healthy control and entire RRMS group, or than those and between the healthy control and cognitively intact RRMS groups. Lower premorbid intelligence, as assessed by the WTAR, may be one of the contributing factors to these significant cognitive differences, as the cognitively intact group may have greater cognitive reserve, although education level was the same in both groups. The mean EDSS score was significantly lower in the

cognitively intact group, as was age and duration of MS, possibly reflecting less neuropathology. This may allow for greater neuronal compensation for damage by transferring cognitive functions to more intact brain areas (Fuchs et al., 2019; Schwartz et al., 2013). Since MRIs were not conducted on these groups and there were no details of further activities that enrich the brain leading to greater cognitive reserve, these theories for the difference between the groups remain speculative.

In sum, between group data showed that the cognitively impaired RRMS group was significantly slower, and made more errors, than the cognitively intact groups on the two versions of the SDMT and the Stroop, and there was greater difference between the scores both on the SDMT with and without distractors and the Stroop with and without distractors. The highest significance was observed on the SDMT with distractors and then the Stroop with distractors. It is known that MS participants are susceptible to task disruption and difficulty in inhibiting these distractions as evidenced in the Gorilla in the Room test (Feinstein et al., 2012). The differences between the cognitively intact and impaired groups is likely due to the differences in EDSS scores, duration of disease and WTAR scores.

Group Comparisons within the Cognitively Intact and Cognitively Impaired Relapsing Remitting Multiple Sclerosis Groups: Two Versions of the SDMT and the Stroop

Within group comparisons revealed that both the impaired and intact RRMS groups performed significantly more poorly on the SDMT with distractors than the SDMT without distractors, and similarly on the Stroop with distractors compared to the Stroop without distractors.

These results support the study's within group hypotheses and establish that the SDMT and the Stroop with distractors have greater sensitively in detecting cognitive impairment across

both relapsing remitting groups than the same tests without distractors. The present research also established the sensitivity of the SDMT, which is consonant with MS literature emphasizing the SDMT as the most sensitive measure of cognitive impairment (Benedict et al., 2017; Brochet et al., 2008; Fuchs et al., 2022; van Schependom et al., 2014).

Although, not a primary focus of the study, comparisons within the cognitively intact and impaired RRMS groups revealed that the healthy control group performed significantly worse on the SDMT with distractors and the Stroop with distractors. The profiles of the healthy control and cognitively intact RRMS group were very similar, which will be evaluated in the following segment. Overall, these results reveal the significant impact of the distractors on processing speed in all groups, attesting to the greater sensitivity of the SDMT and the Stroop with distractors.

Cognitively Intact Relapsing Remitting Multiple Sclerosis and Healthy Control Groups

The central aim of this research was to investigate whether auditory distraction impacts information processing speed in people with RRMS who test as cognitively intact on the MACFIMS compared to healthy controls. The cognitively intact RRMS group in the present study were cognitively strong and significantly better on the D-KEFS sorting and description subtests than the healthy control group, which revealed superior verbal and spatial concept formation, problem-solving and ability to categorize. This may also indicate that the D-KEFS is a less sensitive test of cognitive impairment. However, there were no significant differences between these groups on the rest of the MACFIMS indices, the SDMT (with and without distractors) or on the Stroop (with and without distractors) on initial comparison (using Criterion 1, failure of three out of 11 indices on the MACFIMS). Despite the increased specificity on the SDMT (88.8% to 93.3%) and the Stroop (88.8% to 91%), both with distractors, at detecting impairment in the

cognitively intact RRMS group, this group fared similarly to the healthy controls on both versions of both tests. The SDMT had the highest sensitivity among all 14 tests (67.5%) in detecting impairment in the cognitively intact RRMS group. Additionally, as noted previously the greatest percentage difference between the healthy control group and the total RRMS group was on the SDMT with distractors. However, this difference was not revealed between the healthy control group and the cognitively intact RRMS group. Although a counterbalance methodology was utilized to mitigate possible practice effects there was also the possibility that the dual role of the SDMT (which will be explained in the next section) might have had an influence on the SDMT results.

Global Impairment Based on Two Criteria

There was a concern that was noted in the research design that the administration of the SDMT and the Stroop twice within a two-and-a-half-hour period could result in practice effects that could affect the results. It is unusual that the same test is administered twice in a battery unless it is for research purposes. In research on the SDMT practice effects have been noted (Brochet et al., 2008; Benedict et al., 2008; van Schependom et al., 2014). With monthly testing over a year on the SDMT performance improved by 1.2 points in the first six months and by 0.4 points over the last six months (Roar et al., 2016). A retrospective of analysis of a database of 740 people with MS (mostly RRMS) who had been tested on the SDMT multiple times showed an improvement with repeated exposure, likely reflecting practice effects which were magnified when the SDMT was tested with briefer intervals. Results suggested a 1.8-point improvement on the SDMT with each administration (Fuchs et al., 2019). The authors recommended a solution in using validated SDMT tests that have different symbols corresponding with the nine numerals,

that is, alternative versions of the test. This was not possible in the present research as SDMT outcomes may have been confounded had two different SDMTs had been utilized. The extent of possible practice effects on the SDMT is unclear since other research using the SDMT with monthly administrations over five months showed minimal practice effects (Drake et al. 2010). In order to mitigate the potential confounding effects of the two administrations, a counterbalance methodology was applied in the current research design. However, there was also another possible confounding effect that became evident, that of the dual roles of the SDMT, as part of the MACFIMS battery, and as a dependent variable with the inclusion of the distractors. In order to evaluate whether or not this was a factor the SDMT was removed from the MACFIMS analyses so that only 10 indices remained. Impairment was then based on three out of 10 indices and this was referred to as Criterion 2. When Criterion 2 was used to distinguish the cognitively impaired and cognitively intact RRMS groups the number of participants in each group changed. The cognitively impaired RRMS group decreased from 33 to 28 and the cognitively intact group increased from 46 to 51. The following section discusses the result of the between group comparisons of the healthy control group and the cognitively intact group using Criterion 2.

Comparisons between the Healthy Control Group and Cognitively Intact RRMS Group using Criterion 2

Demographic comparisons between the above groups were similar to those between the healthy control group and total RRMS group. The only differences were on employment and HADS scores, with the cognitively intact group having significantly higher unemployment and mental health scores than the controls. There were no significant differences on nine out of the 11 indices on the MACFIMS. The cognitively intact group was in fact significantly stronger on the

two of the executive functioning indices, the D-KEFS sorting and description, revealing a cognitively able group. No significant differences were discerned on any of the error scores for the two versions of the SDMT and the Stroop. This held true both when using Criterion 1 and Criterion 2. However, when Criterion 2 was used, the healthy control group was significantly faster than the cognitively intact RRMS group on both versions of the SDMT. This highlighted the subtle cognitive impairment of the cognitively intact RRMS group in processing speed, despite their cognitive strengths in other areas. Although both versions (with and without distractors) of the SDMT produced similar significant results, the greater sensitivity of the SDMT with distractors was evident in the within group comparisons where the two RRMS groups fared significantly poorer on the distractor version.

Although the cognitively intact RRMS group showed little impairment compared to the healthy control group and in fact exhibited superior executive skills on the D-KEFS sorting and description subtests, they have brain pathology, albeit subtly, impacting their cognition that was unmasked by poorer performance on the SDMT. There are substantial neurophysiological differences between healthy controls and people with MS when engaged in tasks involving information processing that are observed on fMRI. People with MS that exhibited slower information processing used different neural circuitry compared to controls particularly when cognitive load is increased. There was a compensatory increase in brain activation in the prefrontal cortex and right temporal gyri with a concomitant decrease in activity in the left temporal gyri (Smith et al., 2012). The next section touches on neurological pathology that assists in the explanation of the differences found between the intact RRMS group and the healthy controls on the SDMT and the Stroop (with and without distractors).

Neurological Correlates of Cognitive Impairment

There are strong neurological correlates with functioning on the SDMT and the Stroop. Normal functioning connectivity is important for the maintenance of intact cognition in MS and when this connectivity breaks down there is associated cognitive impairment (Fuchs et al., 2019; Yu et al., 2012). Although both grey and white matter lesions are found early in the disease process in RRMS there are more white matter lesions than cortical lesions (Todea et al., 2020). There is a strong connection between white matter structural damage with high lesion occurrence and slower information processing speed, which is a predictor of poor SDMT performance (Rossi et al., 2012). The SDMT is highly sensitive at detecting cognitive impairment as it is often the strongest correlate of brain MRI pathology (Drake et al., 2010; Silva et al., 2019). Studies have also utilized the Stroop test to assess cognition in relation to nerve fibre functioning. Information processing speed depends on the brain to rapidly transfer information in its neural network. Slower processing speed and executive function have been associated with white matter tract functionality, especially inhibition which is demonstrated in the Stroop test (Santiago et al., 2007; van Geest et al., 2018). The detection of neuropathology at the earliest stage of MS is a likely explanation for significantly impaired performance of the intact RRMS group on the SDMT. Since more white matter lesions are evident early on in MS, these interfere with efficient nerve conduction and relaying of information. Although the intact RRMS group had minimal disability and was cognitively similar to the healthy controls, and even superior on some executive skills, they were significantly slower at information processing. Thus, the SDMT is particularly sensitive to this pathology as evident in the results obtained. Conversely, the Stroop although a sensitive measure of information processing speed is less so than the SDMT.

The next section discusses the results of the present study in relation to various theoretical models including the Relative and Independent Consequence Models (DeLuca et al., 2004), the Load Perception theory (Lavie, 1995, 2005, 2010) and the changing-state hypothesis (Hughes et al., 2013; Korner et al., 2019; Roer et al., 2014; Sorquist, 2010a).

Research Results and Theoretical Implications

The results found on the SDMT revealed that information processing is significantly slowed down even in those with MS who exhibited minimal disease burden. These results corroborate other studies that cite decreased information processing speed as one of the earliest and most ubiquitous of all cognitive difficulties in MS (Chiaravalloti & DeLuca, 2008; Denney et al., 2004; Denney et al. 2008; Eizaguirre et al., 2018; Hughes, Denney et al., 2013). Speed of information processing also decreases with disease duration. (Costa et al., 2017). This was born out in the present study which revealed that the cognitively impaired RRMS group had a significantly longer mean disease duration of 3.86 years and were significantly slower than the intact RRMS group on the SDMT (with and without distractors; P<.001) and the Stroop (with and without distractors; $p < .001$). As MS progresses greater abnormalities in normal appearing white matter emerge, which affect neural integrity and result in deficits in information processing speed. These factors then impact other cognitive domains (Archibald & Fisk, 2000; DeLuca et al., 2004; Parmenter, Shucard et al., 2007). The cognitively impaired RRMS group had an EDSS one point greater than the cognitively intact RRMS group and although regarded as mild, signifies additional disability. They also had MS for 5 years longer than the cognitively intact group, potentially adding to disease load. With the results obtained from this study is not possible to categorically state that impairment in speed of information processing underlies difficulties in other domains of

cognitive processing including working memory as is postulated in the Relative Consequence Model (DeLuca et al., 2004). However, the results of this study reveal that very early on in the disease process, cognitively intact people with RRMS with minimal disease burden, exhibit impairment in information processing speed, but not in verbal and visual immediate and delayed memory and learning, nor in some executive functions (verbal and spatial problem-solving and categorizing), spatial orientation and verbal fluency compared to the healthy control group. The results in this group point towards the strong explanatory power of the Relative Consequence Model early in the disease process. With a small increase in disease burden as is the case with the cognitively impaired RRMS group, significant differences become apparent between the impaired and intact groups in all 14 of the cognitive tests, including errors on the two versions of the SDMT and the Stroop. Thus, a number of cognitive domains are impaired compared to the intact RRMS group, such as learning and immediate and delayed memory in verbal and visual domains, decreased information processing speed, spatial orientation and word fluency. Also evident are greater difficulties in working memory, attention and executive functions in terms of inhibitory control. This supports the Independent Consequence Model which proposes that although impairment in information processing speed is significant, the other domains, specifically working memory are impaired, which may be due to the development of different areas of neuropathology, such as axonal degeneration and increased abnormalities in normal appearing white matter (DeLuca et al., 2004). Thus, early in the MS disease process both neuropathological areas of information processing speed and working memory may well be affected. This would have to be confirmed on MRI however, the procedure is often unavailable due to many factors, such economic considerations and availability of MRI machines, and so the reliance on sensitive and

valid neuropsychological testing is vital to discern and monitor disease progression. Due to neurobiological correlates that have already been established in a number of neuropsychological tests, deficits on these tests may provide insight into brain pathology (Altermatt et al., 2018; Amin et al., 2021; Batista et al., 2012; Chung et al., 2018; Di Filippo et al., 2018; Dong et al., 2022; Eilam-Stock et al., 2021; Figueroa-Vargas et al., 2020; Filippi et al., 2010; Genova et al., 2009; Hulst et al., 2013; Koini et al., 2016; Noncentini et al., 2014; Papadopoulous et al., 2013; Penny et al., 2013; Riccitelli et al., 2019; Silva et al., 2019).

In the current study, the information processing speed deficits found in the total RRMS group, particularly in the cognitively impaired group, but also in the intact group highlight the effect of embedded irrelevant speech distraction on speed of information processing. Although only two of the three serial information processing tests used in the present study have embedded distractors for reasons that have previously been provided, the results of the PASAT – 2 and PASAT – 3 in this study rely heavily on working memory function, which is dependent on speed of information processing. The cognitively intact RRMS group did not appear impaired in working memory as there was no significant difference between this group and the healthy controls on the two versions of the PASAT. However, the cognitively intact group had significantly higher scores on the PASAT compared to the cognitively impaired RRMS group. Since the PASAT taps into working memory it is likely that difficulties with working memory were unmasked in the cognitively impaired RRMS group.

One of the most common explanatory theories of working memory, the Multicomponent model (Baddeley & Hitch, 1974, 2019), maintains that working memory has temporal limits and capacity limits on information processing. Irrelevant speech uses capacity in the phonological loop

and people with impaired working memory capacity are particularly affected on such tasks (Adams et al., 2018; Hughes, Hurlstone et al., 2014). This is a plausible explanation for the cognitively impaired RRMS group's significantly poorer performance on both versions the SDMT and the Stroop and particularly on the distractor versions of the SDMT in speed of information processing and accuracy compared to the cognitively intact group.

Further theoretical investigation is required to explain the differences between the two RRMS groups. The cognitively intact group was largely able to overcome possible difficulties in working memory as evidenced by comparisons with the healthy control group. However, the distractors did slow down information processing speed in the cognitively intact group. Perceptual Load Theory (Lavie, 1995, 2005) maintains that the processing of information is dependent on the amount of information that is being received and the difficulty of the focal task. This theory also states that when the cognitive load is low then material irrelevant to the task at hand will enter into working memory for processing. Neither the SDMT nor the Stroop are cognitively taxing, however, the addition of auditory distractors adds to perceptual load and requires greater selective attentional resources. Perceptual processing is automatic, not under voluntary control, provided there is available capacity. Therefore, all stimuli are processed, even those not required for the target task. This in turn draws on attentional resources, which are limited in capacity, slowing down information processing (Eayrs & Lavie, 2021; Lavie, 2005; Lavie 2010; Lavie & Hirst, 2004). This theory provides an explanation for the slowing of information processing speed in the SDMT and the Stroop that was evident in the RRMS groups. The healthy control group not impeded by MS disease burden was able to withstand the auditory distraction more efficiently.

Related to the above explanation of additional drains on attentional resources, the attentional network of the brain operates when attention is involuntarily directed towards perceptual stimuli as is the case with auditory distraction (Cowan, 2008; Petersen and Posner, 2012). The processing of perceptual stimuli involves three phases; alerting, orienting and selecting. Incoming sensory stimuli are automatically processed for novel or deviant aspects. Then an involuntary orientation of attention is triggered to evaluate new sensory information, and third, reorientation to the task at hand follows only using information that is relevant to the target task (Berti, 2013; Getzmann et al., 2022). The first two stages are involuntary, automatic bottom-up responses, and the last is voluntary, a top-down response (Petersen & Posner, 2012). Irrelevant unintelligible speech elicits an automatic semantic processing response, a bottom-up automatic diversion of attention to the distracting sound. It is potent enough to linger for a period in working memory and interfere with selective attention to a target task (Bell et al., 2011; Lutfi-Proctor, 2016). This obligatory processing has cognitive consequences and can result in delayed response time and decrease in accuracy on a given task, since both distractor processing and cognitive tasks compete for the same cognitive resources (Berti, 2013; Liebl et al., 2016; Romei et al., 2001; Sorquist, 2010a). In people with MS there is an impairment in attentional control exposing attentional network deficits (Crivelli et al, 2012; Urbanek, 2010; Wojtowicz et al., 2013). The alerting and orientating mechanisms (P3) in individuals with RRMS is impaired and there is evidence that it is the demyelinating process that underlies delayed latencies on ERP tests (Vázquez-Marrufo et al., 2014). If a distractor has a speech-like component, is complex and long in duration, as was the case in the present study, it impairs performance speed and accuracy (Diamond et al., 1996; Diamond et al., 1997; McCarthy et al., 2005). Irrelevant speech is a

distractor of this type, particularly linguistically discernable words as compared to tones or nonsense syllables, which are different kinds of distractors (LaPointe et al., 2005). The reason for the strong automatic response to speech-like distractions is that there are continuous changes from one distractor sound to another resulting in recurring attentional shifts. Changing-state sound sequences, such as the embedded speech in the current study, cause more interference in attention than single deviation sequences (Hughes, 2014; Korner et al., 2019; Roer et al., 2014). This is evident in the present research as both the cognitively intact and impaired groups performed significantly slower than the healthy controls on the tests with imbedded unintelligible speech distractors. This finding is in contrast to those of a study that assessed the impact of distractors on people with MS (Patel et al., 2017). The distractor sounds that were embedded in the SDMT were telephone rings and car horns, which are sounds that are regarded as deviant and not changing-state (Korner et al., 2019). No differences were noted between performance on the SDMT and the SDMT with distractors, although the MS participants were significantly slower on both versions of the test than the healthy control participants. Deviant sounds, although distracting can cause an automatic attentional capture away from a target task, but are subject to top-down attentional control and habituation to the sounds may occur, whereas changing-state sequences are relatively immune to top-down attentional control (Hughes et al., 2014; Parmentier, 2008). The results of the present study confirm the potency of unintelligible speech in reducing processing speed and also importantly, accuracy on the SDMT and the Stroop. In doing so, they serve as a powerful means of evaluating slowed information processing in people with RRMS, who are cognitively intact.

Strengths and Limitations of the Study

There are a number of strengths in the present research. The research was innovative and unique in that the distractor literature in MS is small and none of the existing studies focus on the RRMS cohort. The group with RRMS in the present study had minimal disease burden and so a substantial number were identified with intact cognitive functioning according to the MACFIMS. Thus, the sample size was adequate and met the threshold for the Central Limit Theorum for the statistical analysis (Salkind, 2012). This provided a sufficiently representative sample of people with RRMS, both in the cognitively intact and cognitively impaired groups. It affords statistical robustness for future use of the SDMT and Stroop with distractors as screening tools and also to monitor cognitive status over time. The research design involved standardized embedded distractors in terms of duration and auditory volume in the Stroop and SDMT. This ensured a uniform delivery of distractors to each participant and allows for future standardized use of these measures in English-speaking populations. The added sensitivity that was found in these tests in unmasking cognitive dysfunction is diagnostically helpful for rehabilitation purposes and to provide individuals with an insight into their functioning.

The current research can be easily replicated in the future as the MACFIMS was used, which is regarded as the 'gold standard' for the assessment of cognitive functioning in people with MS. Each of the indices has been validated and translated in a number of languages and the MACFIMS as composite has been validated in many countries (Benedict et al., 2006; Gromisch et al., 2018; Grossi et al., 2020; Parmenter et al., 2010). Importantly, the MACFIMS has been validated in Canada where the study took place (Berard & Walker, 2022; Walker et al., 2017). In sum, the present research acts as a methodological template for the worldwide development,

validation and application of the distractor versions of the SDMT and the Stroop. This is potentially a valuable contribution provided by the present study.

The SDMT is regarded as the sentinel test in MS for revealing deficits in information processing speed (Akbar et al., 2011; Benedict et al., 2017; Fuchs et al., 2022; Healy et al., 2021). The present research has added ecological validity to this test and strengthened its ability to detect subtle cognitive impairment in the RRMS population. The Stroop is one of the most common rapid serial processing tests used in MS (Denney and Lynch, 2009). As a test it also reveals an enhanced interference effect in people with MS, in addition to impaired speed of information processing (MacNiven et al., 2008). The addition of the distractors amplifies the interference component of the test enabling it to further reveal disruption in focused attention and consequent impaired performance on a focal task.

A further strength of this research is the inclusion of theories such as the Perceptual Load Theory (Lavie 1995, 2005), the Multicomponent Model (Baddeley & Hitch, 1994, 2019) and the changing-state hypothesis (Hughes et al., 2013; Korner et al., 2019; Roer et al., 2014; Sorquist, 2010a). These theories are rarely if ever referenced in MS research in which the approach is predominantly empirical and quantitative. The present study has provided greater explanatory power by contextualizing the results obtained with cognitive psychology theory. This enrichment provides a template for the expansion of the sparse theoretical literature in auditory distraction in MS and additionally a model for multidisciplinary discussion.

There are also limitations in this study, which warrant mention. The RRMS course was selected as the focus of research to obtain a sample of individuals who were cognitively intact. In this disease course physical disability is mild to moderate and more individuals are cognitively

intact than impaired (Heled et al., 2021). This is especially the case in the current research where the mean EDSS was 2.04 out of a ten-point scale. There are however, people with SPMS and primary PPMS who also test as cognitively intact. These people were not part of the study due to many possible confounding factors. Therefore, extrapolation of the study results to the entire MS population cannot be made. A study containing people from these MS subtypes could further elucidate the effect of distractors on speed of information processing in cognitively intact people in other MS subtypes, providing diverse profiles.

One of the major difficulties and limitations this study faced was possible practice effect. Both versions of the SDMT and the Stroop were administered within a two-and-a-half-hour timeframe. The practice effect potentially affected all groups, including the healthy controls. In order to mitigate this influence on the distractor versions of the two tests, a counterbalance methodology was implemented. Even though practice effects conceivably occurred, significant differences were still found in the within group analyses in both the cognitively intact and impaired RRMS groups attesting to the power of the embedded distractors.

There was also a potential limitation with greater complexity. The SDMT was both part of the MACFIMS and a dependent variable in the distractor version of the test. The SDMT as a sentinel test in MS is a component of each of the most widely used and internationally validated neuropsychological assessment batteries, namely, the BNB-R, the MACFIMS and the BICAMS. Since these tests are all aimed at revealing cognitive deficits in the areas most affected by MS using any of them would have the same limitation. In order to control for possible practice effects, the SDMT as part of the MACFIMS was statistically removed from the statistical analyses, and the results revealed significant differences between the cognitively intact RRMS group and the

healthy control group on both versions of the SDMT. This held true, albeit that the cognitively intact RRMS group was largely similar to the healthy control group, with the exception of their executive skills, which revealed superior verbal and spatial concept formation, problem-solving and ability to categorize compared to the healthy controls.

The following are additional limitations of the study. Hearing was not formally assessed before testing commenced. Individual participants as well as their treating neurologists were questioned about hearing acuity. If no difficulties were reported it was taken that hearing was sufficiently intact to pick up sounds within the normal range at which the irrelevant speech was pitched. Thus, hearing was not considered as a confounder. The WTAR which assesses premorbid IQ is regularly used in MS research. It has been standardized with Wechsler Adult Intelligence Scale and Wechsler Memory Scale, which have been validated in Canada. The WTAR has not been specifically validated in the Canadian population, but has been used in research in the Canadian MS population (Patel et al., 2017; Patel & Feinstein, 2019).

In comparison to existing MS research on cognition, this study contained a reasonable sample size, however, a larger sample may yield a cognitively intact MS group that is even more representative of RRMS cognitive functioning. This could potentially produce stronger results on the distractor versions of the SDMT and Stroop.

Conclusion

Multiple sclerosis, an autoimmune disorder, is one of the most widespread, disabling, neurological disorders impacting 2.8 million people in the world (The Multiple Sclerosis International Federation, 2020). It affects a younger adult population that other neurodegenerative disorders with subsequent ramifications for career development, financial stability, social and

occupational functionality, and quality of life (Browne et al., 2014; DeLuca & Enzinger, 2017). A disproportionate number of people with MS are unemployed, with 80-90% of individuals leaving the workforce within the first five years after diagnosis (Strober et al., 2013; Strober, 2020). Consequently, not only is there a personal impact, but society as a whole loses potentially valuable members of its workforce who are in the prime of their careers. Cognitive impairment, which is one of the first symptoms of MS, with the rate of impairment at 45%-60% and a lifetime prevalence closer to 50-75%, is a significant mediating factor in job loss in MS and contributes more to attrition from work than physical disabilities (Amato et al., 2010; Bøe Lunde et al., 2014; Campbell et al., 2017; Deloire et al., 2011; Filippi et al., 2018; Macaron et al., 2020; Morrow et al., 2010; Strober et al., 2014). Cognitive impairment often develops early in the disease course, when demyelination first occurs, and once cognitive deficits are detected they tend to be linked to more extensive cognitive disability years later (Amato, Portaccio, Goretti, Ziploi, Hakiki, et al., 2010; Deloire et al., 2010; Deloire et al., 2011; Eilam-Stock et al., 2021; McNicholas et al., 2018). An early expression of cognitive decline can be observed in the areas of information processing speed, attention and working memory and these may be the first symptoms of MS, with information processing speed underlying other cognitive deficits (DeLuca et al., 2004; Chiaravalloti & DeLuca, 2008; Costa et al. 2017; Glanz et al., 2012). Given the consequences of cognitive impairment on productivity and quality of life in people with MS, considerable research has been devoted to neuropsychological assessment. This has driven the imperative to develop concise psychometric batteries such as, the BNB-R, the MACFIMS and the BICAMS, to measure the most common cognitive deficits in MS. If an assessment is performed early in the MS disease course, a clinician has information about possible cognitive impairment with concomitant decline

over time, and associated neurological pathology. This can all inform selection of treatment planning, as well as monitoring the progression of the disease.

The MACFIMS is the most comprehensive of the MS neuropsychological batteries and is used to assess the most common deficits in MS, namely, reductions in speed of information processing, verbal and visual memory, attention and executive functioning (Adler & Lembach, 2015; Sumowski et al., 2018). Importantly, the present research corroborated the results of many previous studies citing these impairments (Amato, Portaccio, Goretti, Zipoli, Hakiki, et al., 2010; Berrigan et al., 2013; Deloire et al., 2011; Eilam-Stock et al., 2021; Johnen et al., 2017; McNicholas et al., 2018; Noncentini et al., 2006; Ruet, Deloire, Charre-Morin, et al., 2013). The current study not only adds to the body of neuropsychology research by confirming previous results, but is in turn validated by these studies.

The present research focused on speed of information processing, which is the cognitive domain that is most impacted from an early stage of MS even before physical disability is apparent (Eftekhari et al., 2017). The aim of the present study was to investigate the effect of auditory distraction on speed of information processing in people with RRMS, by embedding unintelligible speech in the computerized versions of the SDMT and the Stroop. Irrelevant speech was used as the distraction medium to introduce ecological validity to the study, as the majority of studies are undertaken in a quiet distraction-free space that does not mimic real-life situations (Patel et al., 2017; Randolph et al., 2017).

The SDMT is regarded as more sensitive than other cognitive tests at detecting information processing speed difficulties in the early stages of MS (Strober et al, 2019). As a single test it is the preeminent predictor of cognitive decline over time (Benedict et al., 2008; Fuchs et al., 2022;

Healy et al., 2021). In the current study, the addition of the auditory distractors significantly increased the sensitivity of the SDMT in detecting slowing of information processing in the cognitively intact and impaired RRMS groups. Both versions of the SDMT (with and without distractors) were the only tests to unmask information processing speed impairment in the cognitively intact RRMS groups compared to the healthy controls. Additionally, within group comparisons in the cognitively intact and cognitively impaired groups revealed that the distractor version of the SDMT was significantly more sensitive at detecting these impairments than the non-distractor SDMT.

The Stroop is frequently used in MS assessments to test speed of information processing, selective attention and inhibitory processes of executive functioning. It is not a particularly cognitively challenging test and requires speed of information processing more than executive functioning facility (Denney & Lynch, 2009; MacNiven et al., 2008). However, the addition of embedded, irrelevant speech distractors both amplified the inhibition component of this test and significantly slowed down speed of information processing, and thus, increased the sensitivity of this test for both the cognitively intact and cognitively RRMS impaired groups. Since the SDMT and the Stroop are so widely used, the added sensitivity of the distractor versions has the potential for extensive neuropsychological application to unmask cognitive deficits not only in MS, but also in other neurological disorders.

The current research showed that cognitive impairment is present even in people with RRMS with minimal disability who test as cognitively intact on the MACFIMS. Yet cognitive impairment is underdiagnosed and undertreated in this population as it is not routinely checked at initial diagnosis nor follow-up appointments (McNicholas et al., 2018). A reason for this

circumstance is that cognitive assessment batteries, such as, the BNB-R, the MACFIMS and the BICAMS, that assess the most common cognitive deficits in MS require time and neuropsychologically trained personnel for their administration. Psychologists and psychometrists are often not available in a clinic setting and many regions of the world are underserved by neuropsychological testing. Consequently, the impetus for the present research, was to further develop two easily administered computerized cognitive tests, the SDMT and the Stroop, that are already highly validated and regularly used in MS cognitive assessments. The distractor versions of these two tests compared to the non-distractor versions were significantly better at revealing deficits in people with MS in information processing speed, selective attention and executive inhibitory responses. An added advantage of these tests is that they are easily available. They can be administered by any staff member to track cognitive status, using a laptop computer or electronic tablet, as scoring is automatically computed. Used either separately (the SDMT is the more sensitive of the tests) or in conjunction, the two tests have the capacity to provide an insight into cognitive impairment in less than ten minutes. Additionally, the SDMT is not language dependent, while the Stroop has been translated and validated in many languages. Distractor irrelevant speech that mimics the cadence and sounds of any language can be embedded into these tests. This would allow for a worldwide use of these sensitive tests.

Although sound is the most potent of the perceptions in terms of its propensity for distraction, surprisingly few studies have assessed the implications of such distractions for cognition in people with MS (Bendixon et al., 2010; Leiva et al., 2015; Patel et al., 2017). Universally, people experience an automatic physiological orientation to sound, especially speech-like sounds, which are changing-state (Berti, 2013; Roer et al., 2014; Parmentier, 2014).

People with RRMS experience difficulty in maintaining focus on a task, especially in the presence of an auditory verbal distractor that is continuous, and reorientation to a task following distraction is delayed compared to healthy controls. An unintelligible speech distractor that is continuous adds to cognitive resource load, resulting in slower information processing speed, as reorientating to a target task following distraction is delayed in people with MS in comparison to healthy controls (LaPointe et al., 2005). In the present study, both the SDMT and the Stroop revealed the difficulty the RRMS groups experienced with inhibition of the speech distractor, which is vital for selective and focussed attention. Additionally, the SDMT was able to show this significant impairment in people with MS who were cognitively intact on the MACFIMS compared to healthy controls. These results were obtained despite the minimal physical disability exhibited by the RRMS group.

There is potentially extensive use for the SDMT and the Stroop with the added sensitivity provided by the distractors. Three major applications stand out. Firstly, there is evidence of significant correlations between cognitive dysfunction as measured by the SDMT and the Stroop, and MRI measures of atrophy, lesion burden and microbrain pathology (Benedict et al., 2012; Benedict et al., 2017; Brochet et al., 2008; Fuchs et al., 2022; Gromisch et al., 2018; Lopez-Gongora et al., 2015). These tests with distractors appear to register subtle impairment early in the disease process and point towards neural pathology, which may then be verified with MRI measures.

Secondly, people with MS are rated for neurological disability by a neurologist using the EDSS, which is rated from 0-10 (Kurtzke, 1983). At times, a patient has negligible physical disability as the MS disease burden is below the clinical threshold, and consequently an EDSS of

0 may be provided (McDonald et al., 2001). This is regarded as 'neurologically normal' (Krieger et al., 2021). Cognitive impairment is not recorded on the EDSS, yet is one of the early symptoms of MS (Amato, Portaccio, Goretti, Zipoli, Hakiki et al., 2010; Eilam-Stock et al., 2021; McNicholas et al., 2018). A second application of these tests used in the current study is that the distractor versions of the SDMT and the Stroop (since they are so sensitive, particularly the SDMT) may be the first evidence of functional decline, even in an individual rated as 0 on the EDSS, and these results could be the catalyst for further investigations.

Thirdly, earlier diagnosis of cognitive impairment can result in effective enrolment in remediation and rehabilitation programs, which can in term result in adaptive neuroplasticity (Chiaravalloti et al., 2015). Propensity to distractibility as revealed on the distractor SDMT and the Stroop can raise awareness in the individual with MS of their difficulties and accommodations can be made in study or work situations. A quiet room in which to work or noise cancelling headphone can enhance selective and focused attention. This in turn may increase performance and result in employment retention or completion of tertiary education. There are also cognitive rehabilitation programs that are effective in improving MS-related cognitive deficits in verbal and visual memory, learning, working memory, information processing, attention and executive functioning in RRMS (Brissart, Leroy et al., 2013; Chen et al., 2021; Mattioli et al., 2016).

The cognitively intact RRMS group in the current study were cognitively able, and more so in executive functioning such as, problem-solving, verbal and spatial concept formation, and flexibility of thinking than the healthy control group. However, they were still significantly slower on both versions of the SDMT compared to the healthy controls. Further research with a larger

cohort of people with early RRMS who are cognitively intact is needed to replicate and confirm these results.

In sum, the present study substantiates the need for highly sensitive, valid neuropsychological tests to diagnose cognitive impairment early in MS. With the use of the SDMT and the Stroop (both with distractors) taking just a few minutes, the ramifications and value for early detection of cognitive deficits (in terms of slower speed of information processing, selective and focused attention impairment, and executive inhibitory responses) are significant. Results from these tests can inform a neurologist of neural pathology, which may then be verified by physical examination, imaging and EPR tests. Insight can be provided to an individual with MS concerning the status of their cognitive performance, which may help in an educational or work setting to provide accommodations for retention and success in those situations. It may also result in rehabilitation programmes, the development of compensatory strategies and concomitant neuroplasticity, which are potentially invaluable in daily functioning.

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APPENDICES

Appendix A: Kurtzke Expanded Disability Scale (EDSS)

Score	Description of Symptoms
0.0	Normal neurological exam (all grade 0 in all Functional System (FS) scores*).
1.0	No disability, minimal signs in one FS* (i.e., grade 1).
1.5	No disability, minimal signs in more than one FS* (more than 1 FS grade 1).
2.0	Minimal disability in one FS (one FS grade 2, others 0 or 1).
2.5	Minimal disability in two FS (two FS grade 2, others 0 or 1).
3.0	Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory.
3.5	Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3 (others 0 or 1) or five grade 2 (others 0 or 1).
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combination of lesser grade exceeding limits of previous steps; able to walk without aid or rest some 500 meters.
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability usually consisting of one FS grade 4 (others or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 300 meters.
5.0	Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions); (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0).
5.5	Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions); (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0).
6.0	Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions); (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0).

6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting; (Usual FS equivalents are combinations with more than two FS grade 3+).
7.0	Unable to walk beyond approximately 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day; (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely pyramidal grade 5 alone).
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair; (Usual FS equivalents are combinations with more than one FS grade 4+).
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms; (Usual FS equivalents are combinations, generally grade 4+ in several systems).
8.5	Essentially restricted to bed much of day; has some effective use of arm(s); retains some self-care functions; (Usual FS equivalents are combinations, generally 4+ in several systems).
9.0	Helpless bed patient; can communicate and eat; (Usual FS equivalents are combinations, mostly grade 4+).
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow; (Usual FS equivalents are combinations, almost all grade 4+).
10.0	Death due to MS. *Excludes cerebral function grade 1.

Note 1: EDSS steps 1.0 to 4.5 refer to patients who are fully ambulatory and the precise step number is defined by the Functional System score(s). EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation and usual equivalents in Functional Systems scores are provided.
Note 2: EDSS should not change by 1.0 step unless there is a change in the same direction of at least one step in at least one FS. (Kurtzke, 1983)

Appendix B: Informed consent form to take part in study

INFORMED CONSENT TO PARTICIPATE IN A RESEARCH STUDY
Full Study Title: The Impact of Auditory Distraction on Processing Speed in Multiple Sclerosis

Principle Investigator: Dr. A. Feinstein, Department of Psychiatry
In collaboration with the University of the Witwatersrand, South Africa, Professor. Kate Cockcroft, Department of Psychology (supervisor), Karen Redhill-Feinstein PhD candidate.
Sponsor: This study is being funded by the Multiple Sclerosis Society of Canada

INFORMED CONSENT

You are being asked to consider participating in a research study. A research study is a way of gathering information on a treatment, procedure or medical device or to answer a question about something that is not well understood.

This form explains the purpose of this research study, provides information about the study, the tests and procedures involved, possible risks and benefits, and the rights of participants.

Please read this form carefully and ask any questions you may have. You may take as much time as you wish to decide whether or not to participate. Please ask one of the researchers to clarify anything you do not understand or would like to know more about. Make sure all your questions are answered to your satisfaction before deciding whether to participate in this research study.

INTRODUCTION

You are being asked to consider participating in this study because you have a diagnosis of Multiple Sclerosis (MS). MS is the leading cause of neurological disability in young and

middle-aged adults. The prevalence rate of MS in Canada is high with approximately 70,000 individuals affected. Of these, up to 40% may have cognitive (intellectual) problems as a result of the disease.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to determine whether auditory distraction has a significant impact on cognition in MS. Cognitive difficulties in people with MS can lead to problems in the workplace, socially, in decision-making and daily activities of life, which often result in reduced quality of life. By understanding the role of auditory distraction in cognition we may come to further understand the complex causes of cognitive problems in MS. If auditory distraction is found to be a contributor to impairments in tasks of cognition certain strategies may be put into place to reduce auditory distraction.

WHAT WILL HAPPEN DURING THIS STUDY?

During the testing session here, you will be asked to answer a questionnaire about your demographic information such as age, marital status, and occupation as well as your medical and psychiatric history. Then you will be asked to complete a battery of neuropsychological tests assessing cognitive functions such as memory as well as psychological states such as depression and anxiety.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Approximately 80 people MS and 50 healthy individuals will take part in this study. The entire study is expected to take about two years to complete.

WHAT ARE THE RESPONSIBILITIES OF STUDY PARTICIPANTS?

In order to be eligible for this study you must have a diagnosis of MS. For this study, you will be asked to complete several tests of cognitive and psychiatric functioning. This will require approximately

2 ½ -3 hours of your time.

WHAT ARE THE RISKS OR HARMS OF PARTICIPATING IN THIS STUDY?

You may or may not find the cognitive tests challenging.

WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?

You may or may not benefit directly from participating in this study. Results from the neuropsychological tests can be provided to your neurologist. Any deficits revealed through the testing may be used by your neurologist to assist in providing you with appropriate treatment and care.

CAN PARTICIPATION IN THIS STUDY END EARLY?

You can choose to end your participation at any time by informing the research assistant. A refusal to participate will not lead to any loss in treatment or penalty.

WHAT ARE THE COSTS OF PARTICIPATING IN THIS STUDY?

This study will require approximately 2½ -3 hours.

ARE STUDY PARTICIPANTS PAID TO PARTICIPATE IN THIS STUDY?

You will be given $20 to cover parking and transportation costs.

DOES(DO) THE INVESTIGATOR(S) HAVE ANY CONFLICTS OF INTEREST?

No

CONFIDENTIALITY

Your identity will be kept confidential by ascribing a unique number to your research results.

WHAT ARE THE RIGHTS OF PARTICIPANTS IN A RESEARCH STUDY?

All participants in a research study have the following rights:

1. You have the right to have this form and all information concerning this study explained to you and if you wish, translated into your preferred language.

2. Participating in this study is your choice (voluntary). You have the right to refuse to participate, or to stop participating in this study at any time without having to provide a reason.

3. You have the right to receive all significant information that could help you make a decision about participating in this study. You also have the right to ask questions about this study and your rights as a research participant to have them answered to your satisfaction, before you make any decision. You also have the right to ask questions and to receive answers throughout this study. If you have any questions about this study you may contact the principle investigator, Dr. Anthony Feinstein (Anthony.feinstein@sunnybrook.ca) and researchers Karen Redhill-Feinstein (karenredhillfeinstein@gmail.com) and Viral Patel (viral.patel@mail.utoronto.ca) If you have questions about your rights as a research participant or any ethical issues related to this study that you wish to discuss with someone not directly involved with the study, you may call Dr. Brian Murray, Chair of the Sunnybrook Research Ethics Board at (416) 480-6100 ext. 88144.

4. By agreeing to participate in this study, you do not give up any of your legal rights.

5. You have the right to receive a copy of this informed consent package before participating in this study.

6. You have the right to be told about any new information that might reasonably affect your willingness to continue to participate in this study as soon as the information becomes available to the study staff. This may include new information about the risks and benefits of being a participant in this study.

7. No personal information will be collected or obtained from this study.

8. You have the right to be informed of the results of this study once the entire study is complete.

DOCUMENTATION OF INFORMED CONSENT

Full Study Title: The Impact of Auditory Distraction on Processing Speed in Relapsing – Remitting Multiple Sclerosis

Name of participant: _____

Participant

By signing this form, I confirm that:

- This research study has been fully explained to me and all of my questions answered to my satisfaction
- I understand the requirements of participating in this research study
- I have been informed of the risks and benefits, if any, of participating in this research study
- I have been informed of any alternatives to participating in this research study
- I have been informed of the rights of research participants
- I have read each page of this form
- I have agreed to participate in this study or agree to allow the person I am responsible for to participate in this study
- I understand that my neurologist will be informed of my participation in this research study
- This informed consent document will be placed in my medical records

_____	_____	_____
Name of participant (Print)	Signature	Date

Person obtaining consent

By signing this form, I confirm that:

- I have explained this study and its purpose to the participant named above
- I have answered all questions asked by the participant
- I will give a copy of this signed and dated document to the participant

_____	_____	_____
Name (Print)	Signature	Date

Statement of Researcher

I acknowledge my responsibility for the care and well-being of the above participant, to respect the rights and wishes of the participant as described in this informed consent document, and to conduct this study according to all applicable laws, regulations and guidelines relating to the ethical and legal conduct of research.

_____	_____	_____
Name (Print)	Signature	Date

Appendix C: The Impact of Auditory Distraction on Processing Speed in Multiple Sclerosis. Demographic questionnaire

---

Study identity number: _____

1. Gender:

☐ Female

☐Male

2. Date of birth: _____(MM/D/Y)

3. Marital status:

☐ Single

☐ In a relationship

☐ Married

☐ Widowed

☐ Divorced

☐ Common-law

4. Highest level of eduation:

☐ High school: years _____

☐ College: years _____

☐ Bachelors: years _____

☐ Post-Graduate: years _____

5. Working?

☐ Yes ➔ Occupation _____

☐ No

6. In what year did your **symptoms** of MS begin? _____

7. In what year were you actually **diagnosed** with MS? _____

a. **Confirmation of disease course**: relapsing-remitting multiple sclerosis ☐ (neurologist to confirm)

b. **EDSS** _____ (neurologist to give score)

8. Do you have a family history of MS? ☐ Yes ☐ No

9. Do you have any other **neurological disease**?

☐ No _____

☐ Yes ➔ _____

10. Have you had a **head injury**? ☐No ☐ Yes ➔

_____

_____

_____

11. Do you have any **hearing difficulties**? ☐No ☐Yes

➔ _____

_____

_____

11. Have you had any **neuropsychological tests** in the past year?

☐ No

☐Yes

➔_____

13. Have you ever been diagnosed with a **psychiatric illness**? ☐ No

☐ Yes ➔ When was this in relation to your MS?

☐ Before my MS

☐ After my MS

☐ Before and after my MS

14. **Diagnosis:**

☐ Bipolar disorder or mania

☐ Substance abuse

☐ Anxiety Disorder
☐ Schizophrenia
☐ Other, please specify_____

15. Do you currently or have you in the past 3 months used **illicit drugs (non- prescribed)**?
☐ Opiates (morphine, codeine, heroin)
☐ PCP
☐ LSD
☐ Stimulants
☐ THC (marijuana) ➔ if yes: frequency
_____
☐ Amphetamines (Methamphetamine, MDA/MDMA)
☐ Benzodiazepines ➔
_____
☐ Barbiturates ➔
_____

16. **Alcoholic drinks** per week: ☐ No ☐ Yes ➔ how many
_____

17. Are you currently taking any **disease modifying drugs**?
☐ No
☐ Yes ➔
_____

18. Are you taking any **other medications**?
☐ No
☐ Yes ➔ names of medications and if related to MS or not _____
_____
_____

19. Are you currently involved in any **other study**? ☐ No ☐ Yes ➔
_____
_____

Appendix D: Participant Information Sheet

The Impact of Auditory Distraction on Processing Speed in Multiple Sclerosis

Hello,

You are being asked to consider participating in a research study, because you have a diagnosis of relapsing-remitting multiple sclerosis (MS). A research study is a way of gathering information on a treatment, procedure or medical device or to answer a question about something that is not well understood. Please read through this information sheet to get an idea about the proposed research and the potential value it will have in adding to our knowledge of cognitive impairment in MS.

MS is the leading cause of neurological disability in young and middle-aged adults. The prevalence rate of MS in Canada is high with approximately 70,000 individuals affected. Of these, up to 40% may have cognitive (intellectual) problems as a result of the disease.

The purpose of the present study is to determine whether auditory distraction has a significant impact on cognition in MS. Cognitive difficulties in people with MS can lead to problems in the workplace, socially, in decision-making and daily activities of life, which often result in reduced quality of life. By understanding the role of auditory distraction in cognition we may come to further understand the complex causes of cognitive problems in MS. If auditory distraction is found to be a contributor to impairments in tasks of cognition certain strategies may be put into place to reduce auditory distraction.

Your participation is voluntary. If you choose to participate you will be asked to answer a questionnaire about your demographic information such as age, marital status and occupation as well as your medical and psychiatric history. There will be a pre-screening, as well, of your eye sight. If you meet the criteria for the study, you will be asked to complete a battery of

neuropsychological tests assessing cognitive functions, as well as psychological states such as depression and anxiety. This will require approximately 2 ½ -3 hours of your time. You may or may not benefit directly from participating in this study. Results from the neuropsychological tests can be provided to your neurologist. Any deficits revealed through the testing may be used by your neurologist to assist in providing you with appropriate treatment and care.

Please direct any questions you may have about the study to:

Researchers:

Karen Redhill-Feinstein (karenredhillfeinstein@gmail.com), PhD Candidate

Viral Patel (viral.patel@mail.utoronto.ca) Research Co-ordinator

Principle investigator:

Dr. Anthony Feinstein (Anthony.feinstein@sunnybrook.ca Professor, Department of Psychiatry, University of Toronto

Research Collaborator:

Professor Kate Cockcroft, (Kate.Cockcroft@wits.ac.za) Department of Psychology, University of the Witwatersrand, South Africa

Thank you for your time.

Appendix E: Advertisement to recruit MS participants

Calling for People with MS to Volunteer for Multiple Sclerosis Research!!

Researchers at Sunnybrook Health Sciences Center are currently developing new methods for assessing cognitive difficulties in people with multiple sclerosis. We are looking for people with relapsing-remitting MS between the ages of 18 - 60 to undergo cognitive testing to help us evaluate assessment new methods. By advancing our knowledge in this field we may better be able to detect cognitive impairment. Participation requires a one-time visit lasting 2 ½ - 3 hours and $20 compensation will be provided. Results of individual cognitive testing will be made available for interested participants.

Where: Sunnybrook Health Sciences Center, 2075 Bayview Avenue, Toronto, ON, M4N3M5

To be eligible to participate:
- must be diagnosed with relapsing-remitting multiple sclerosis
- must be between the ages of 18 and 60

- must **not** have any other brain disease
- must **not** have a history of traumatic brain injury within the past year
- must **not** have a history of any substance abuse (e.g. alcohol)
- must **not** have had neuropsychological testing in the last year

If interested please contact Viral Patel at viral.patel@sunnybrook.ca or 416-480-6100 ext. 7023

Appendix F: Advertisement to recruit healthy controls in MS study

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Calling Healthy Volunteers For Multiple Sclerosis Research!!

Researchers at Sunnybrook Health Sciences Center are currently developing new methods for assessing cognitive difficulties in people with multiple sclerosis. By advancing our knowledge in this field we may better be able to detect cognitive impairment. We are looking for healthy individuals between the ages of 18 - 60 to undergo cognitive testing to help us evaluate assessment new methods. Participation requires a one time visit lasting 2 ½ - 3 hours and $20 compensation will be provided. Results of individual cognitive testing will be made available for interested participants.

Where: Sunnybrook Health Sciences Center, 2075 Bayview Avenue, Toronto, ON, M4N3M5

To be eligible to participate:
- must be between the ages of 18 and 60

- must **not** be diagnosed with multiple sclerosis or any other brain disease
- must **not** have a history of traumatic brain injury within the past year
- must **not** have a history of any substance abuse (e.g. alcohol)
- must **not** have had neuropsychological testing in the last year

If interested please contact Viral Patel at viral.patel@sunnybrook.ca or 416-480-6100 ext. 7023

Appendix G: University of the Witwatersrand Human Research Ethics Committee (Medical) Clearance certificate

R14/49 Ms Karen Redhill-Feinstein

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170502

NAME: (Principal Investigator)	Ms Karen Redhill-Feinstein
DEPARTMENT:	Psychology Sunnybrook, Toronto, Canada
PROJECT TITLE:	The Effect of Auditory Distraction on Processing Speed in Relasping-Remitting Multiple Sclerosis
DATE CONSIDERED:	26/05/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Kate Cockcroft and Prof Anthony Feinstein
APPROVED BY:	Professor P. Cleaton-Jones Chairperson, HREC (Medical)
DATE OF APPROVAL:	21/08/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004,10th floor, Senate House/3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review May and will therefore be due in the month of May each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date August 22, 2017.

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix H: Sunnybrook Health Sciences Centre Research Ethics Clearance

Sunnybrook
HEALTH SCIENCES CENTRE

Research Ethics Office, Room C819
2075 Bayview Avenue
Toronto, ON Canada M4N 3M5
t: 416-480-6100 ext. 4276 or 88144
www.sunnybrook.ca/reo

To: Dr. Anthony Feinstein
Psychiatry
Room FG16

From: Dr. Brian J. Murray

Date: September 8, 2016 (revised)

Subject: **The Impact of Auditory Distraction on Processing Speed in Multiple Sclerosis**

Project Identification Number: 140-2010

The Research Ethics Board is in receipt of your response dated September 7, 2016 pertaining to the above referenced study. A delegated review has been conducted and the following documents have been approved.

- Protocol dated September 6, 2016
- Informed Consent Form for MS Patients dated September 6, 2016
- Informed Consent Form for Control dated September 6, 2016
- Advertisement for MS (**Submit to Communication and Stakeholder Relations for review prior to posting**) (not dated)
- Advertisement for Healthy Participants (**Submit to Communication and Stakeholder Relations for review prior to posting**) (not dated)

This study may continue at Sunnybrook Health Sciences Centre.

During the course of the research, any significant deviations from the approved protocol and/ or any unanticipated developments must be brought to the attention of the Research Ethics Board.

Thank you for keeping the Board informed.

Brian J. Murray, MD FRCP(C) D,ABSM
Chair, Research Ethics Board
/mh

OR

Philip C. Hébert, MD PhD FCFPC
Vice-Chair, Research Ethics Board

The Research Ethics Board of Sunnybrook Health Sciences Centre Operates in Compliance with the Tri-Council Policy Statement 2nd edition, ICH GCP Guidelines, Part C Division 5 of the Food and Drug Regulations, Part 4 of the Natural Health Products Regulations, and Part 3 of the Medical Devices Regulations. All Health Canada regulated trials at Sunnybrook are conducted by a Qualified Investigator.

Fully affiliated with the University of Toronto

Appendix I: Histograms for normality of distribution of demographic, cognitive, mental health variables, EDSS and disease duration variables, Figures 6.1 to 6.8

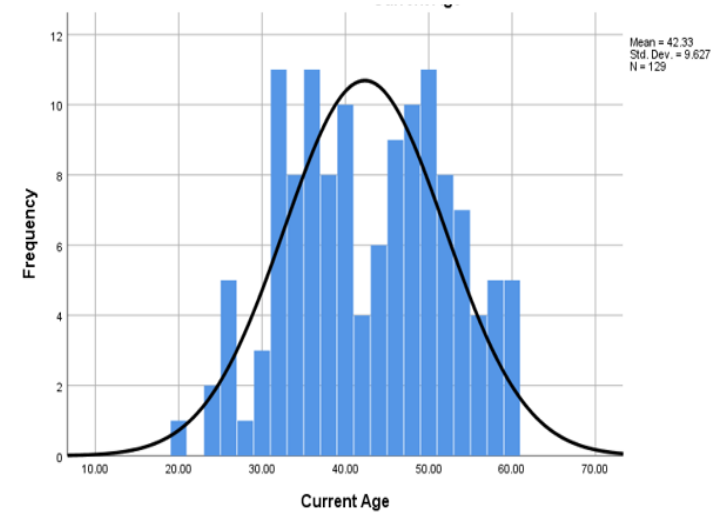


Figure 6.1

Sample Distribution of the Demographic Variable, Age (n = 129)

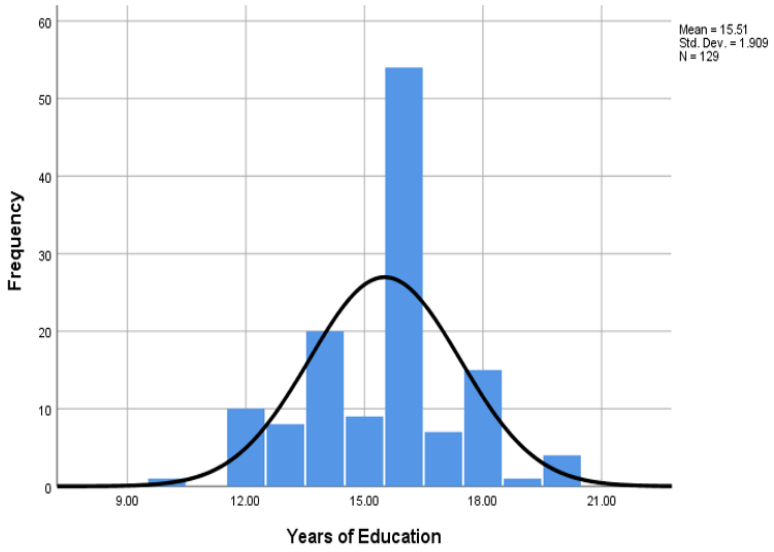


Figure 6.2

Sample Distribution of the Demographic Variable, Years of Education (n = 129)

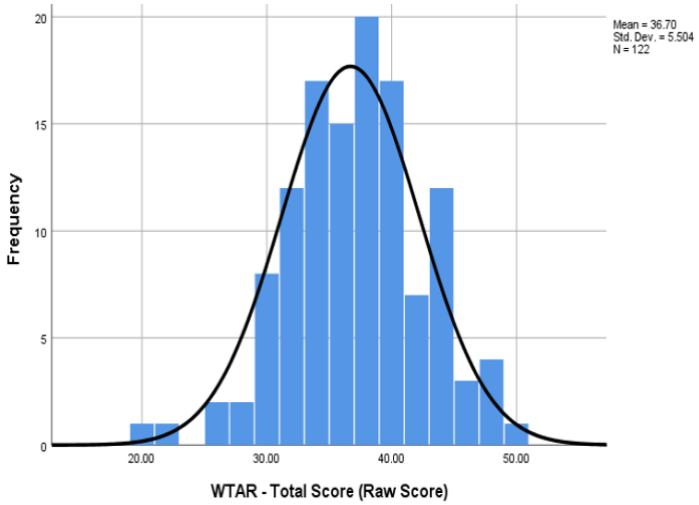


Figure 6.3

Sample Distribution of the Cognitive Variable, WTAR (n=122)

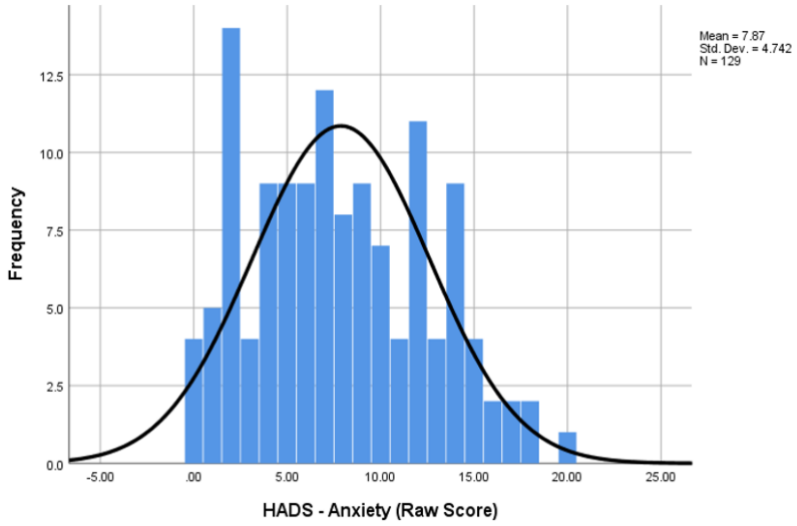


Figure 6.4

Sample Distribution of the Mental Health Variable, HADS Anxiety Score (n = 129)

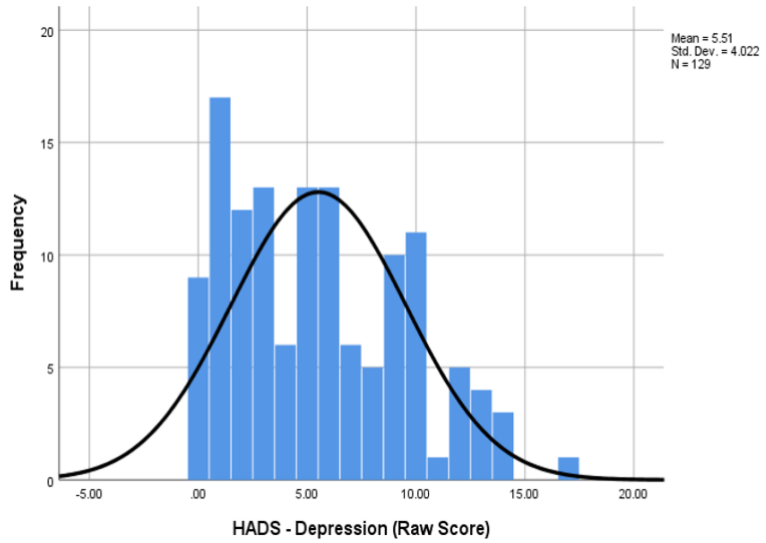


Figure 6.5

Sample Distribution of the Mental Health Variable, HADS Depression Score (n = 129)

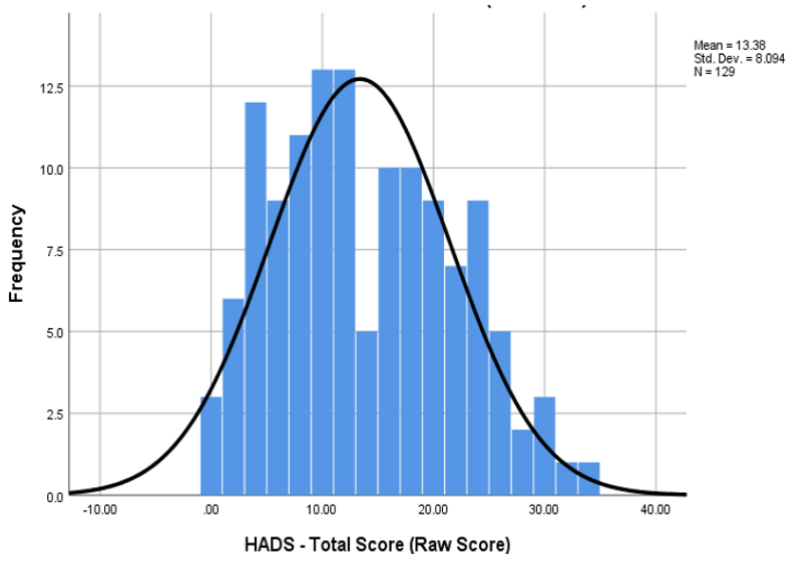


Figure 6.6

Sample Distribution of the Mental Health Variable, HADS Total Score (n = 129)

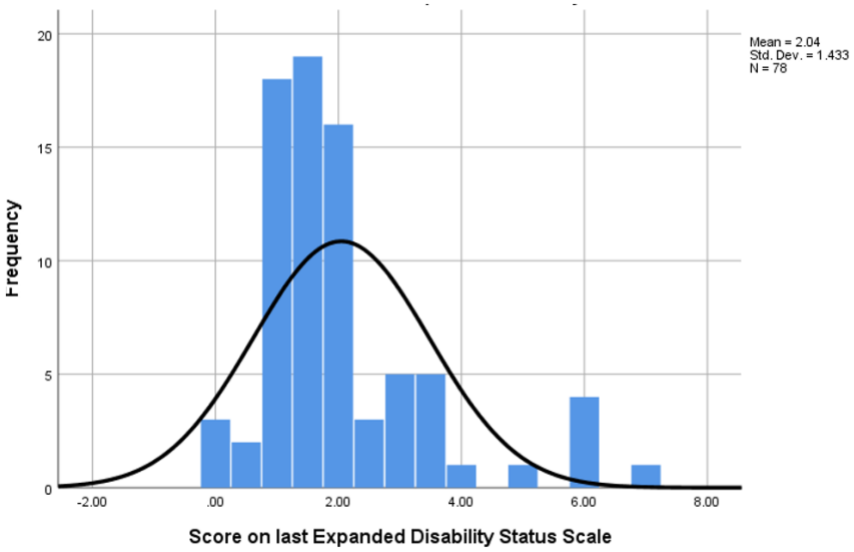


Figure 6.7

Sample Distribution of the Health Variable, EDSS (n = 78)

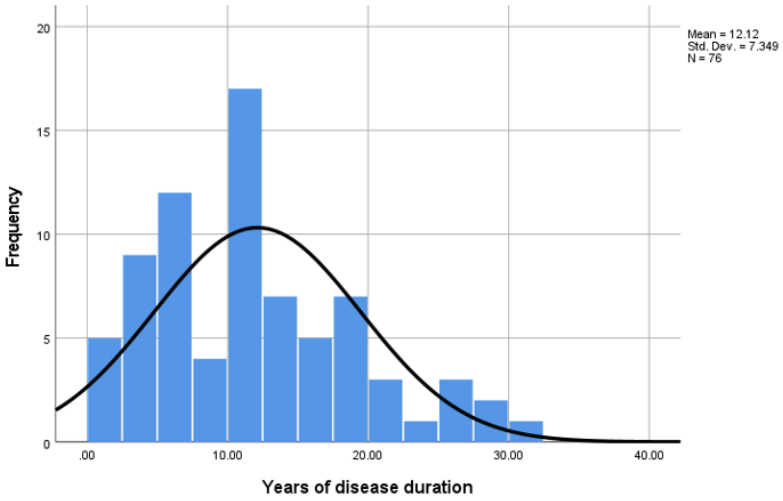


Figure 6.8

Sample Distribution of Years of Disease Duration (n = 76)

Appendix J: Histograms for normality of distribution of the MACFIMS, SDMT with distractors and Stroop, with and without distractors, Figures 6.9 to 6.26

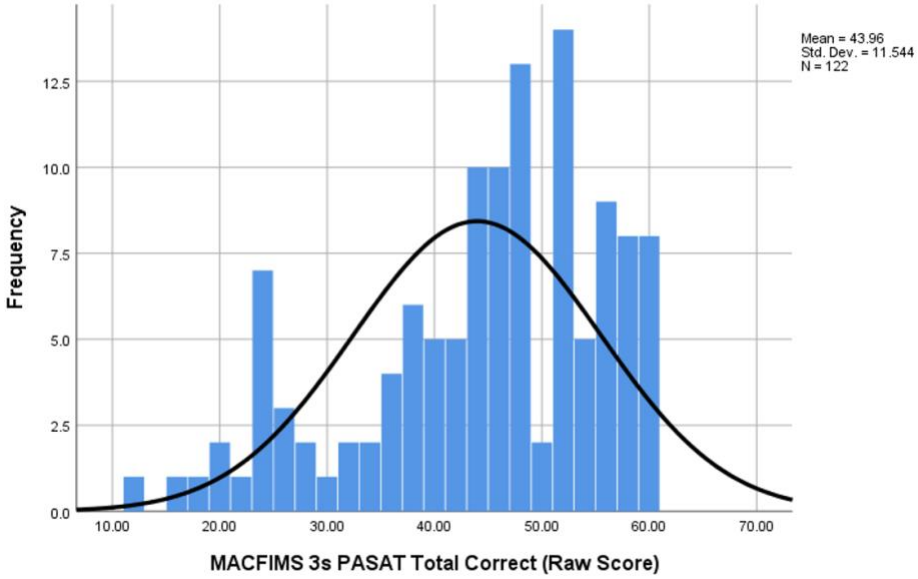


Figure 6.9

Sample Distribution of the MACFIMS Subtest Variable, PASAT – 3 second (n = 122)

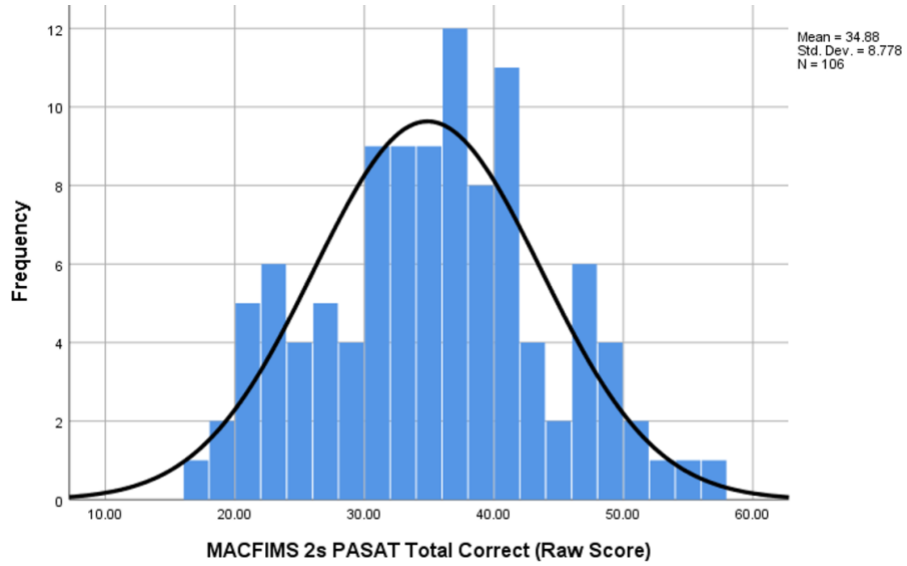


Figure 6.10

Sample Distribution of the MACFIMS Subtest Variable, PASAT – 2 seconds (n = 106)

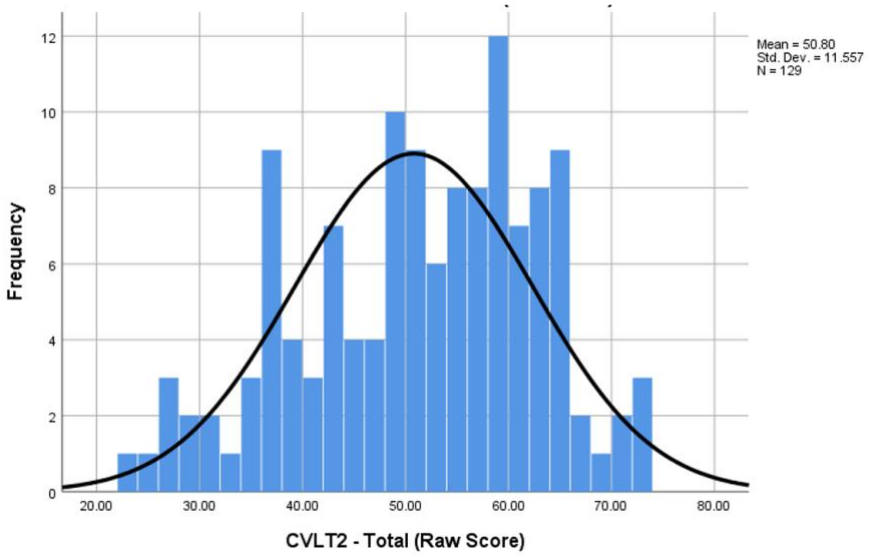


Figure 6.11

Sample Distribution of the MACFIMS Subtest Variable CVLT II-Total (n = 129)

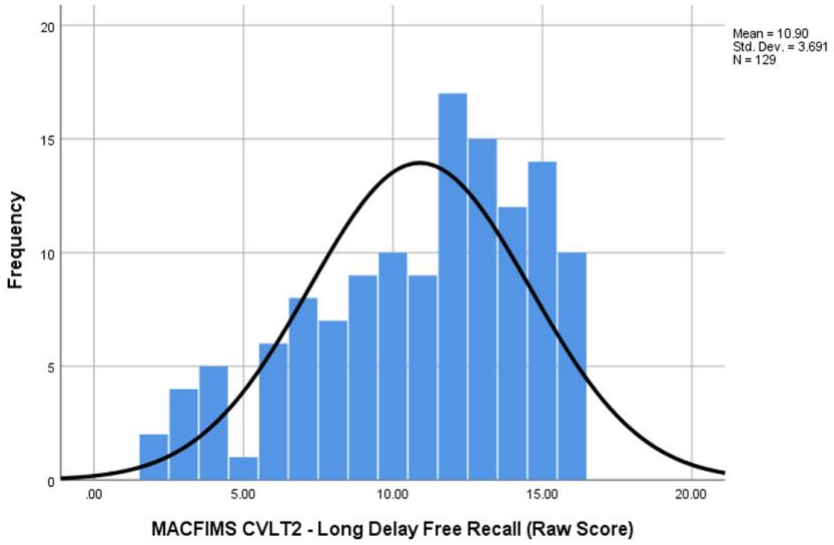


Figure 6.12

Sample Distribution of the MACFIMS Subtest Variable, CVLT II-Delayed Recall (n = 129)

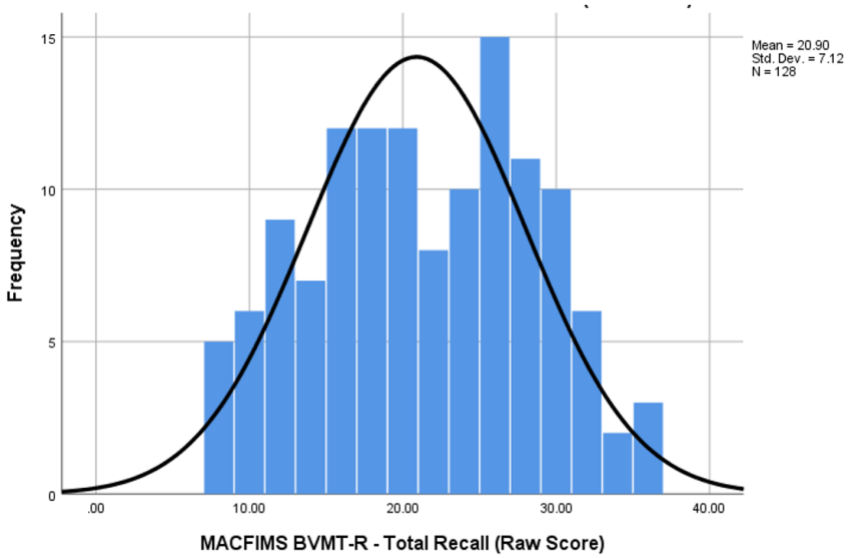


Figure 6.13

Sample Distribution of the MACFIMS Subtest Variable, BVMT-R – total recall (n = 129)

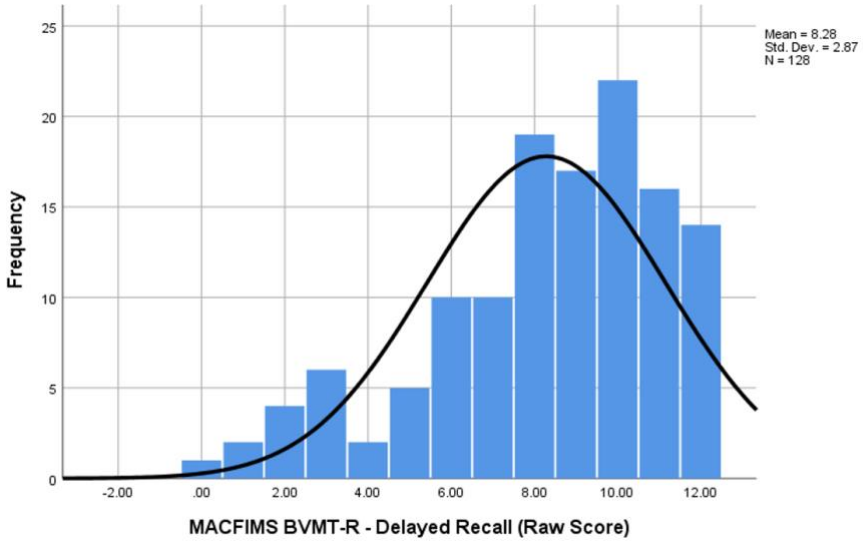


Figure 6.14

Sample Distribution of the MACFIMS Subtest Variable, BVMT-R – delay recall (n = 129)

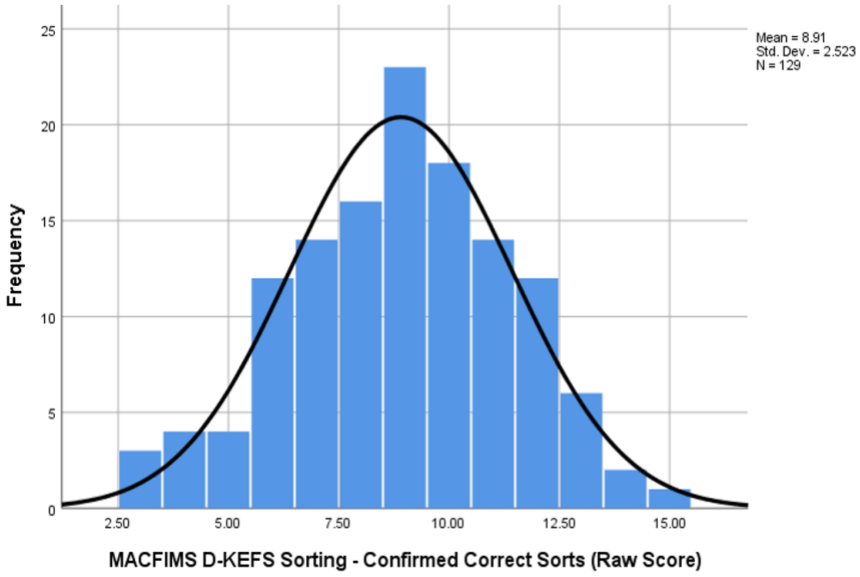


Figure 6.15

Sample Distribution of the MACFIMS Subtest Variable, D-KEFS – Sorting (n = 129)

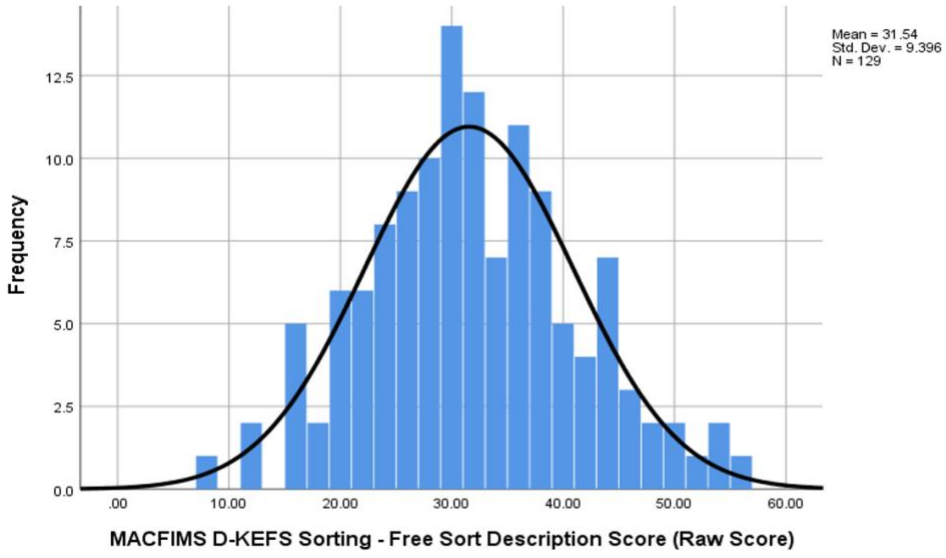


Figure 6.16

Sample Distribution of the MACFIMS Subtest Variable, D-KEFS – Description (n = 129)

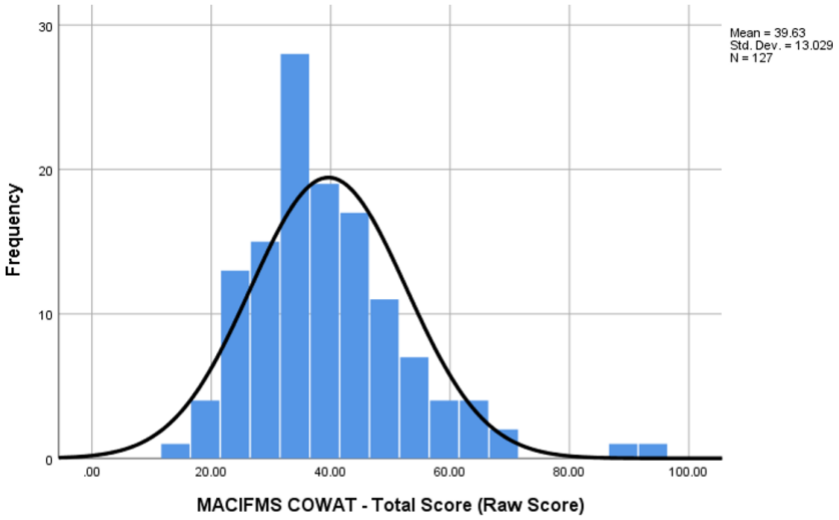


Figure 6.17

Sample Distribution of the MACFIMS Subtest Variable, COWAT (n = 129)

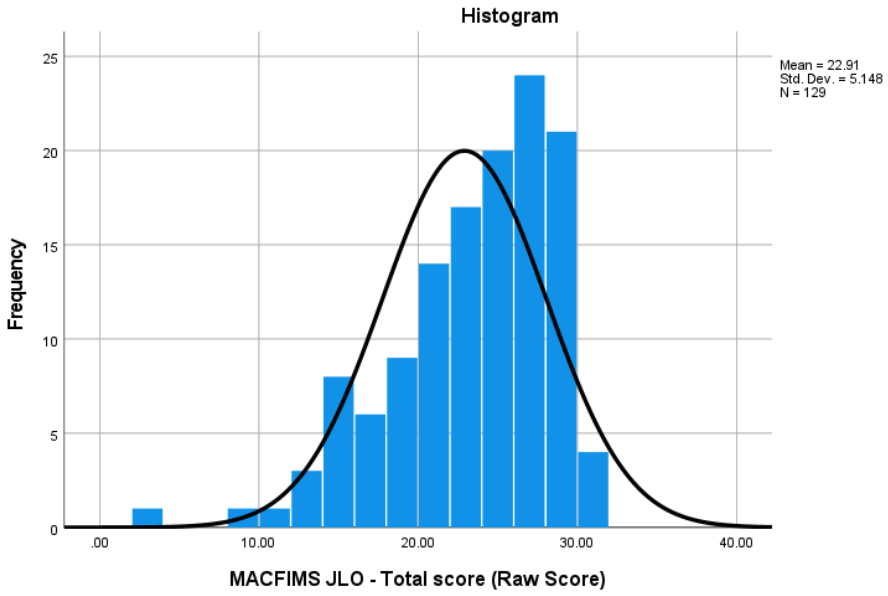


Figure 6.18

Sample Distribution of the MACFIMS Subtest Variable, JLO (n = 129)

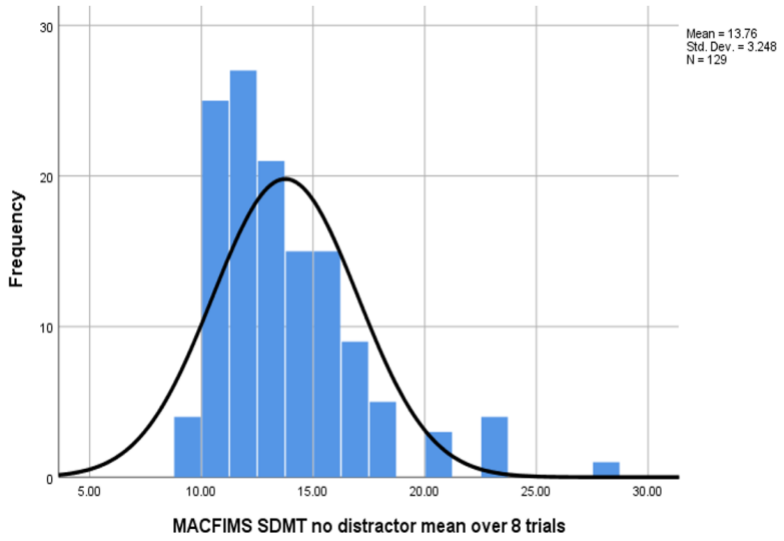


Figure 6.19

Sample Distribution of the MACFIMS Subtest Variable, SDMT, no distractor (n = 129)

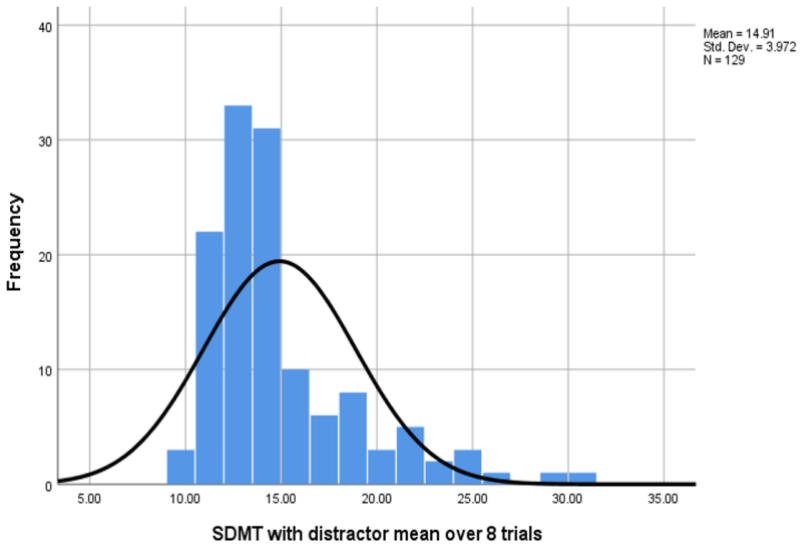


Figure 6.20

Sample Distribution of the Test Variable, SDMT with distractor (n = 129)

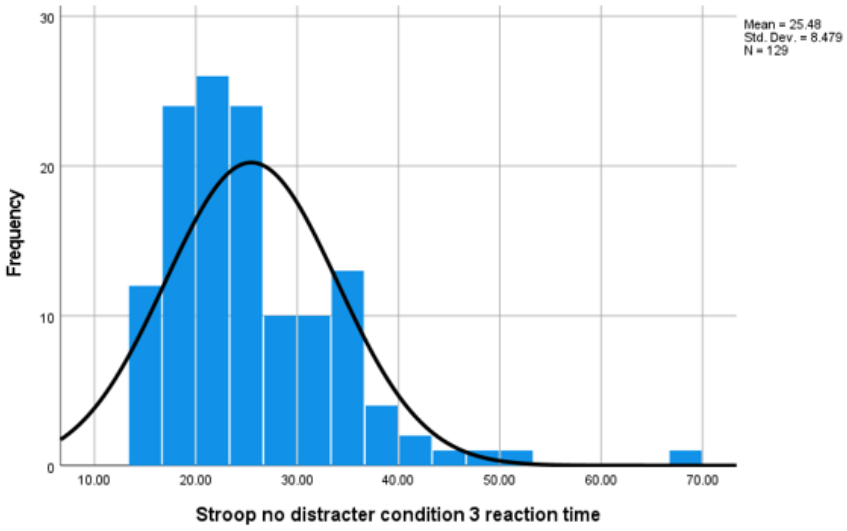


Figure 6.21

Sample Distribution of the Test Variable, Stroop, no distractor (n = 129)

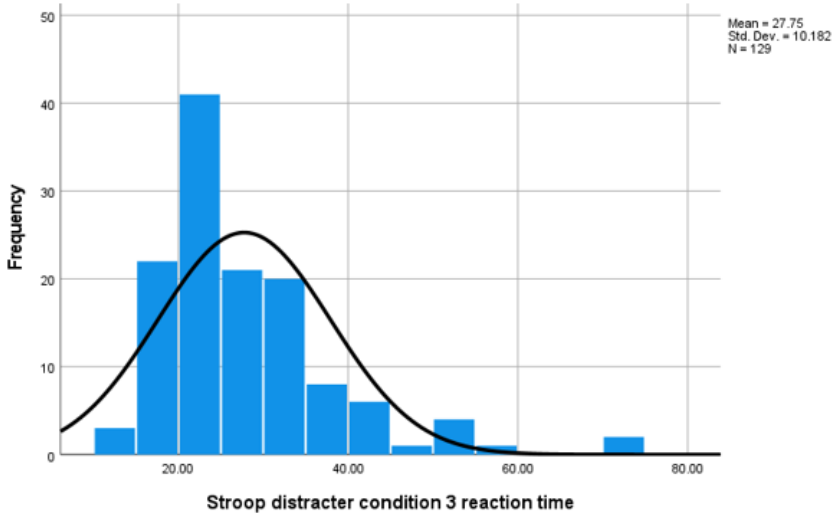


Figure 6.22

Sample Distribution of the Additional Test Variable, Stroop with distractor (n = 129)

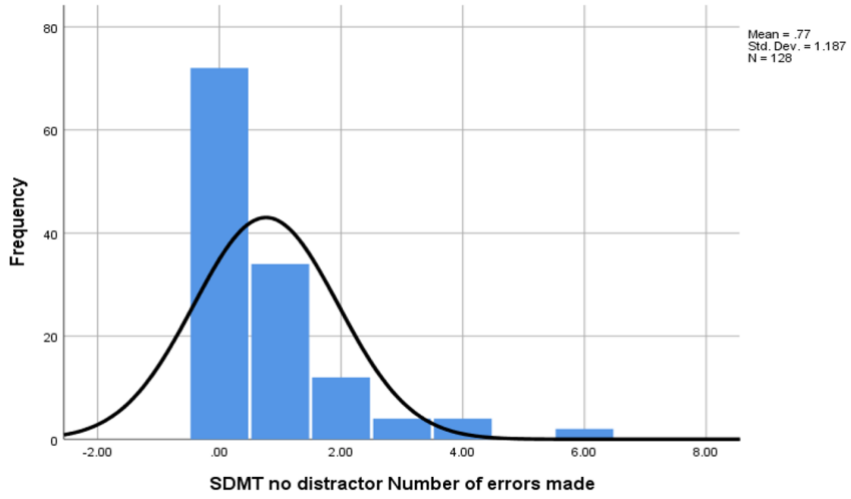


Figure 6.23

Sample Distribution of the Measure, Number of Errors on SDMT, no Distractor (n = 129)

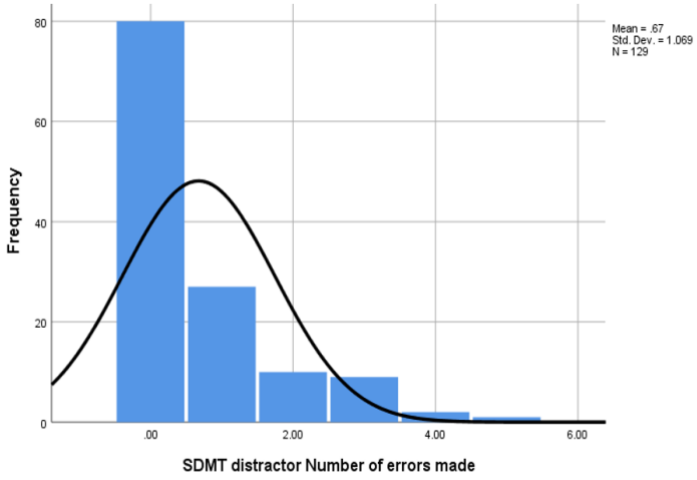


Figure 6.24

Sample Distribution of the Measure, number of Errors on SDMT, with distractor (n = 129)

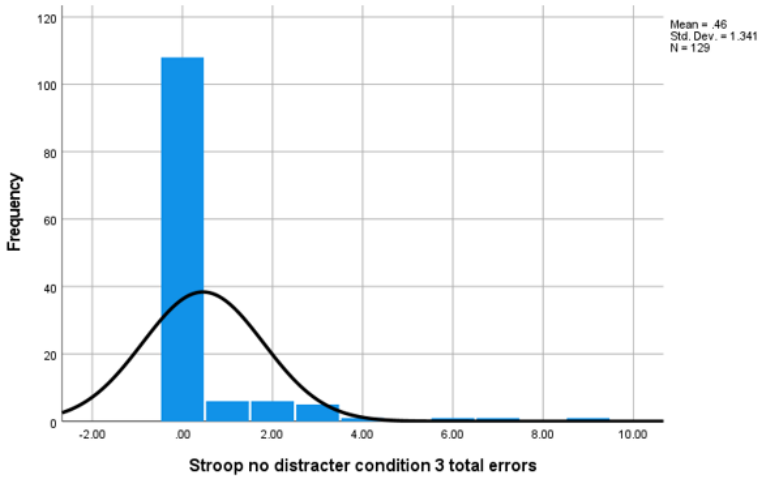


Figure 6.25

Sample Distribution of the Measure, Number of Errors on Stroop, no distractor (n = 129)

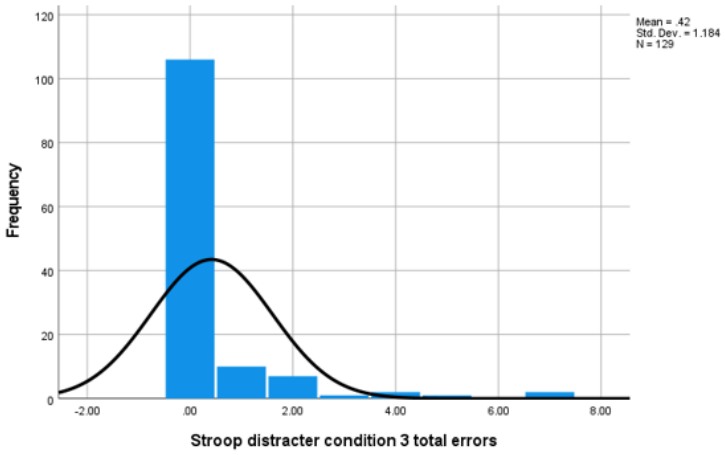


Figure 6.26

Sample Distribution of the Measure Number of Errors on Stroop, with Distractor (n = 129)

Appendix K: Histograms of distribution of the error scores on the, SDMT (with and without distractors) and Stroop, (with and without distractors) in two groups cognitively impaired and intact RRMS - Figures 6.34 to 6.37

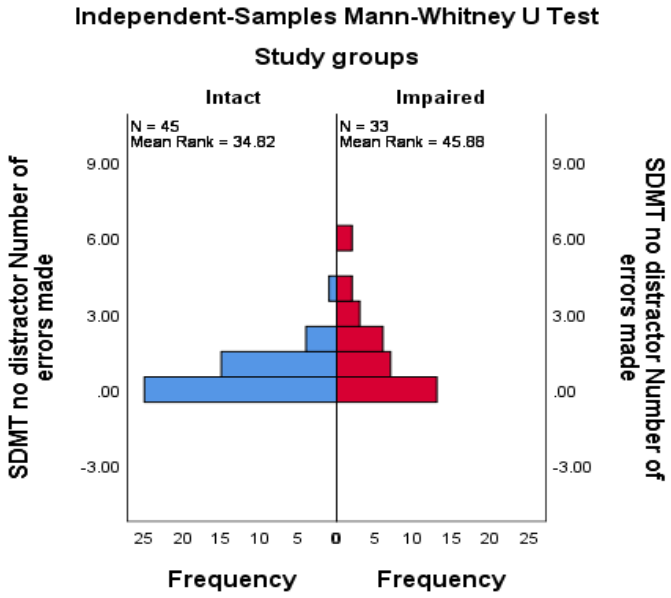


Figure 6.34

Histogram of Number of Errors on the SDMT, without Distractors for the Two Groups, Intact RRMS and Impaired RRMS

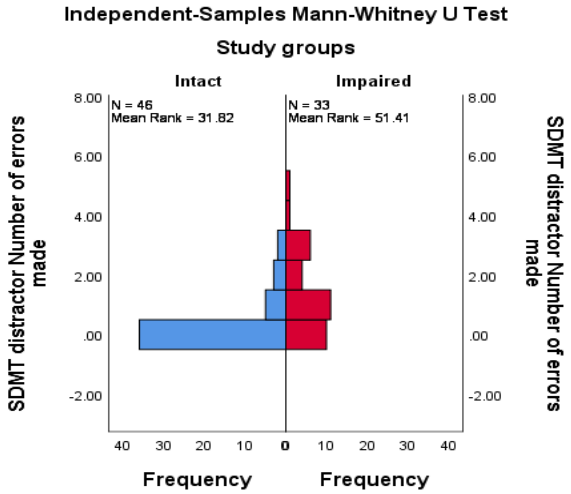


Figure 6.35

Histogram of Number of Errors on the SDMT, with Distractors for the Two Groups, Intact RRMS and Impaired RRMS.

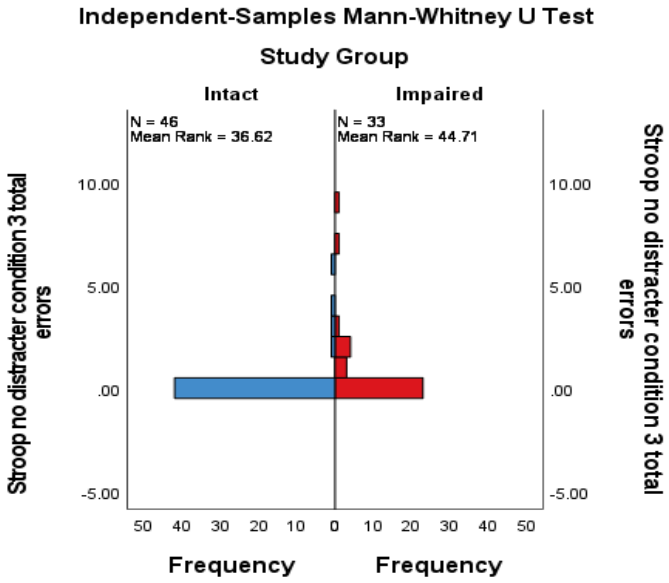


Figure 6.36

Histogram of Number of Errors on the Stroop, (without distractors) for the Two Groups, Intact RRMS and Impaired RRMS

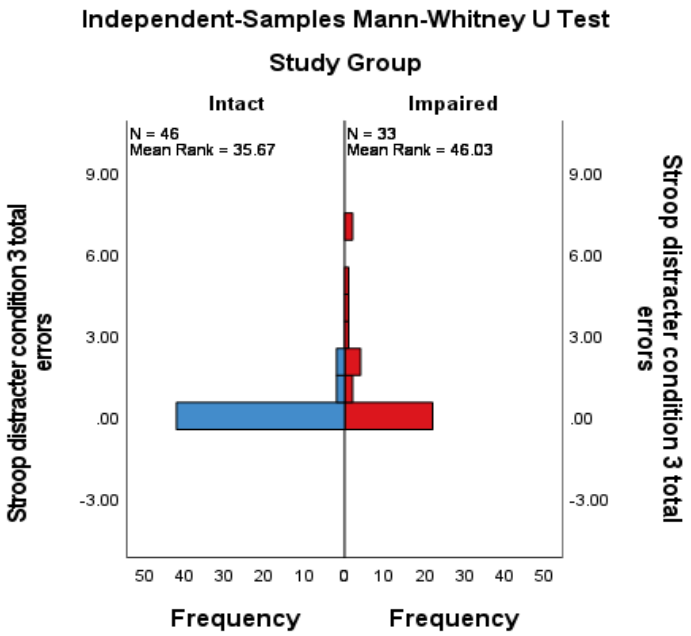


Figure 6.37

Histogram of Number of Errors on the Stroop, with Distractors for the Two groups, Intact RRMS and Impaired RRMS

Appendix L: Table of McDonald Diagnostic Criteria

McDonald Diagnostic Criteria for Multiple Sclerosis*

Clinical presentation	Additional data needed for MS Diagnosis
1. Two or more attacks; objective clinical evidence of two or more lesions *or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack*	None
2. Two or more attacks; objective clinical evidence of one lesion	Dissemination in space, demonstrated by MRI OR Two or more MRI-detected lesions consistent with MS plus positive CSF *2 of 4 MS-typical regions CNS sites (periventricular, juxtacortical infratentorial, or spinal cord)* OR Await further clinical attack implicating a different site
3. One attack; objective clinical evidence of two or more lesions	Dissemination in time, demonstrated by new *T2 lesion on follow up MRI* OR Second clinical attack
4. One attack; objective clinical demonstrated by evidence of one lesion (monosymptomatic isolated syndrome)	Dissemination in space *and time,* MRI OR Second clinical attack presentation *implicating a second CNS site*; Two or more MRI-detected lesions consistent with MS plus positive CSF and dissemination in time, *irrespective of time* demonstrated by MRI *A new T2 lesion or Gadolinium enhanced lesion*
5. Insidious neurological progression suggestive of MS	Positive CSF and dissemination in space, demonstrated by: (1) Nine or more T2 lesions brain, (2) Two or more lesions in spinal cord,

	or, (3) Four to eight plus one spinal cord lesion OR Abnormal visual evoked response (VER) associated with four to eight brain lesions, or with fewer than four brain lesions plus one spinal cord lesion demonstrated by MRI and dissemination in time, demonstrated by MRI OR Continued progression for 1 year *Evidence for DIS in brain based on 1 or more T2 lesion in MS Characteristic regions* *DIS in spinal cord* *Positive CFS*

*Table from Olek, 2005. pp. 18.
** Italic are amendments by Polman et al., 2010