An investigation into the utility of the ImPACT neurocognitive screening tool with patients diagnosed with Multiple Sclerosis

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Abstract

Objective: The objective of this study was to investigate the utility of the Immediate Post Concussion Assessment and Cognitive Testing (ImPACT) assessment tool in the neurocognitive screening of patients with Multiple Sclerosis (MS). **Participants and Method:** Patients diagnosed with Multiple Sclerosis (n = 29) were compared with a healthy control group (n = 20) of equivalent age, years of education, quality of education and estimated premorbid IQ. Measures included five ImPACT composite scores, the ImPACT Design Memory Delayed Recall subtest, the Symbol Digit Modalities Test (SDMT) that has shown prior sensitivity to cognitive dysfunction in MS groups, and the SDMT Delayed Recall test. T-test analyses compared test performances of the MS patient group with the control group; correlational analyses investigated the construct similarities between the ImPACT and SDMT tests. **Results:** There was a consistent trend for the MS patient group to perform worse than controls on all the neurocognitive tests. Significant differences accompanied by medium to high effect sizes were in evidence for ImPACT Reaction Time, ImPACT Cognitive Efficiency Index, ImPACT Design Memory Delayed Recall, SDMT, and SDMT Delayed Recall test. Correlational analyses revealed construct comparability between the ImPACT tests calling upon processing speed and the SDMT, as well as the IMPACT and SDMT delayed recall tasks. **Conclusions:** The results support the utility of the ImPACT test as a screening instrument for the detection of cognitive dysfunction in patients with MS. Tests tapping general cognitive efficiency, processing speed, reaction time, and delayed recall rather than immediate recall reveal particular utility as neurocognitive screening aids for patients with MS.

Declaration

I, Carl Wurz, hereby affirm and declare that the following is my work, and have not been copied or plagiarised from any source without the appropriate reference for such a source. I hereby declare that no harm, to the best of my knowledge, has come to any of the participants of this study as a result of their participation. All reasonable steps have been taken to ensure that no such harm, either personally or otherwise, occurred now and in future to the integrity and wellbeing of the participants and South African society.

30 August 2016 _____

Date *Signature*

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1. Introduction

Multiple Sclerosis, a disorder affecting the central nervous system, is a heterogeneous disease that may result in a wide array of symptoms of varying degrees of severity. These symptoms may include physical impacts (e.g. loss of mobility, loss of vision), emotional impacts (e.g. increased levels of depression) and impacts on aspects of cognition (e.g. memory, attention and processing speed). Although a number of screening tools have been developed to identify and monitor the possible impact of MS on cognition, there is currently no clearly preferred tool in use by neurologists and related health professionals. The Immediate Post Concussion Assessment and Cogntive Test (ImPACT) is a computerised assessment tool that is internationally most widely used in the assessment and monitoring of sports-related mild traumatic brain injuries (Resch, McCrea, & Cullum, 2013).

The primary aim of this study was to do a preliminary investigation into the utility of ImPACT in discriminating between the cognitive performance of patients with MS and healthy controls. The Symbol Digit Modalities Test (SDMT) has previously been shown to have utility as a brief screening test for cognition in patients with MS. This study compared performance on the SDMT and the various ImPACT composite scores. In addition, the use of incidental learning tests was investigated for its ability to discriminate between the cognitive performance of patients with MS and healthy controls. The literature review that follows will provide a background to Multiple Sclerosis, followed by a discussion of its impact on cognition, assessment of cognition in patients with MS and the various tools currently used for such assessment.

2. Background

2.1 Description of Multiple Sclerosis

2.1.1 Introduction

Multiple Sclerosis (MS) is a complex neurological disorder, and is the most common disorder of the central nervous system to cause permanent disability in young adults (Ramagopalan, Dobson, Meier, & Giovannoni, 2010). The disorder is characterised by demyelination and axonal loss within the central nervous system.

Myelin consists of proteins and phospholipids that form a white sheath covering on neuronal axons. The human brain, when compared to other higher primates, has a disproportionately high volume of this white matter (approximately 20%) (Bartzokis, 2004a). Oligodendrocytes are cells that are responsible for the production of myelin. This production of new myelin is a life-long process continuing at least until the age of 50 (see Bartzokis, 2005). Oligodendrocytes produce all of the brain's cholesterol. They have the highest iron content of all brain cell types, and up to 70% of all the brain's iron is associated with myelin (Bartzokis, 2005). This iron is critical in the production of myelin. Myelin facilitates increased axonal transmission speed (> 10-fold), reduces action potential refractory time, and improves synchrony of brain functions (reviewed in Bartzokis, 2002, 2004a). The function of myelin is critically important in facilitating many of the human brain's unique capabilities such as language, inhibitory controls and higher cognitive functions (reviewed in Bartzokis, 2004b).

It is unlikely that MS develops from one particular causative event (Ramagopalan et al., 2010). Rather, genetic predisposition, combined with environmental stressors appears to lead to the development of the disorder (Van Rensburg, Kotze, & van Toorn, 2012). A recent

Mendelian Randomization study has provided evidence that decreased vitamin D level is a causal risk factor for MS (Mokry et al., 2015). Other environmental factors implicated in MS risk are smoking and Epstein-Barr virus infection (van Rensburg et al., 2016). In general, it has been found that the disorder has a very limited impact on life expectancy. The lifespan of patients with MS is only slightly lower than that of the general population at large (Ragonese, Aridon, Salemi, D'Amelio, & Savettieri, 2008). Onset of the disorder is normally between the ages of twenty and forty years, the period normally associated with the highly productive stage of an individual's life. As such it has been shown to often lead to a major negative impact on the health-related quality of life of both the patient and his/her immediate family. The aspects that are compromised include economic, social, and emotional well-being (Jones, Pohar, Warren, Turpin, & Warren, 2008; Koutsouraki & Michmizos, 2014; Moore et al., 2013).

The world-wide prevalence of the disorder is put at more than 2,3 million and can be categorized in three broad geographical zones viz., high incidence regions (prevalence of >30 per 100,000 of the population), medium incidence regions (prevalence of 5 - 30 per 100,000 of the population), and low incidence regions (prevalence of < 5 per 100,000 of the population). South Africa is categorized as a medium incidence region (Browne et al., 2014). It is estimated the prevalence rate of MS in South Africa is put at 5/100,000 (Modi, Mochan, Du Toit & Stander, 2007). The prevalence of the disorder appears to be on the increase. Rosati (2001) is of the opinion that this increase cannot solely be attributed to better identification of the disorder, but that environmental (rather than genetic) factors are probably the driving force behind this increase. The disorder is considered rare in the black population, with one study finding only 12 possible MS cases in blacks from South Africa and Zimbabwe (Dean et al., 1994). Modi et al. (2007) reported an estimated occurrence rate of 3% of all South African MS cases in persons

with mixed ancestry and of Indian descent. The disorder is more common in females with women twice as likely to contract the disorder as men (Kantarci & Wingerchuk, 2006; Orton et al., 2006). The female to male ratio is seen to be rising, possibly due to environmental and social factors such as dietary habits, outdoor activity, and changes in the timing of child-bearing years (Alonso & Hernán, 2008; Orton et al., 2006), with one study (Orton et al., 2006) reporting a ratio in excess of 3,2:1 in Canada.

The developmental course of MS is often erratic and each new attack may involve a different part of the brain or spinal cord white matter, resulting in a great variety of symptoms. A first neurological event with observed demyelination commonly impacts the cerebrum, cerebellum, optic nerves, brain stem or spinal cord (Miller, Barkhof, Montalban, Thompson, & Filippi, 2005). Inflammatory plaques are thought to develop due to a breach in the blood-brain barrier in people with a genetic predisposition to the disorder. These plaques lead to the formation of a demyelinating lesion. The target of the lesions is typically the myelin in white matter, although grey matter lesions, where the myelin is also the primary target, may also occur (Brownell & Hughes, 1962; Frohman, Racke & Raine, 2006).

The accumulation of lesions and neurodegeneration does not impact different areas of the brain in equal measure (Haider et al., 2016). Whereas lesions in the early stages of the disorder can occur at any site in the brain, many of these early lesions may disappear due to resolution of oedema and remyelination. Lesions located in areas of low blood perfusion persist due to a higher degree of tissue damage (Holland et al., 2012). In their seminal study Brownell and Hughes (1962) undertook necropsies on 22 subjects with MS. Their investigation into the distribution of plaques in the cerebrum found that out of a total of 1,594 plaques the areas with the highest concentration of plaques was in the lateral ventricular system (periventricular) (40%),

followed by the frontal lobe (22%), parietal lobe (15%), temporal lobe (12%) and corpus callosum (4%). 74% of the plaques were in white matter, 17% at the junction of the cortex and white matter, and 9% in grey matter. There was no significant difference between the occurrence of plaques between the left and right hemisphere of the cerebrum, with no region appearing to be immune to plaque formation.

Studies such as those by Brownell and Hughes (1962) appeared to support the general view that MS is a disorder primarily affecting white matter. Consequently most research has traditionally been focussed on the impact of the disorder on white matter. More recently however, research of the disorder has moved to its impact on grey matter. Grey matter atrophy has been indicated as a marker of progression of the disorder as it occurs in the early stages of MS and progresses over time to a higher degree than white matter or whole brain atrophy (Pirko, Lucchinetti, Sriram & Bakshi, 2007). A number of studies appear to support the so-called "axonal hypothesis" which proposes that axonal damage and loss due to the disorder is responsible for disability that accrues over time (see Cifelli & Matthews, 2002). Furthermore, cognitive decline in patients with MS has been shown to be more closely related to cortical pathology than to white matter damage (Calabrese et al., 2009; Penny et al., 2013; Sanfilipo, Benedict, Weinstock-Guttman & Bakshi, 2006). The impact of MS on the cortex is heterogeneous, as it may be due to a number of disorder-related factors such as local demyelinating lesions, meningeal inflammation, neuronal injury, and Wallerian or transsynaptic degeneration (Sanchez, Nieto, Barroso, Martin, & Hernandez, 2008), resulting in a heterogeneous presentation of cognitive decline in patients. Therefore, cognition may be spared in some patients with an MS diagnosis.

2.1.2 Diagnosis

The diagnosis of MS is based on clinical abnormalities which are observed in neurological examinations, supplemented by laboratory assessments of aspects such as indications of immune activity in cerebrospinal fluid and evoked potential or MRI studies (Lezak, Howieson, Bigler & Tranel, 2012). There is an emphasis on the dissemination of lesions in both space and time in order to exclude possible alternative diagnoses. It is possible to make a diagnosis based on clinical grounds alone, although the use of MRI scans of the central nervous system generally can "support, supplement and even replace some clinical criteria" (Polman et al., 2011, p. 292). MS has no pathognomonic clinical features or a definitive laboratory test and is based ultimately on a diagnosis of exclusion. A number of other diseases have similar clinical features and can also mimic MS in terms of central nervous system lesions and cerebrospinal fluid abnormalities, which complicates making a final definitive diagnosis. It is estimated that MS is incorrectly diagnosed in 5% to 10% of cases (Gasperini, 2001; Trojano & Paolicelli, 2001). It is important to note that neurocognitive impairment is not a diagnostic criterion for MS diagnosis (McDonald et al., 2001).

2.1.3 Symptoms of the disorder

The disorder is manifested on both a physical and on a cognitive level. Physical symptoms are most often related to lesions in specific sites in the brain and include the following: weakness, stiffness or incoordination of an arm or legs; gait disturbances; visual impairments; neurogenic bladder and bowel symptoms; sexual dysfunction; sensory changes; heat sensitivity and fatigue (Lezak et al., 2012; Rahn, Slusher, & Kaplin, 2012). Cerebellar syndromes also occur in certain instances and may include dysarthria (characterized by thickened, sluggish sounding speech or by spasmodically paced speech), dysphagia (difficulty in

swallowing) and tremor. Common comorbid disturbances of affect and behaviour include affective instability, pathological laughing and crying, and an increase in occurrence of depression and of anxiety (Lezak et al., 2012). A number of studies have shown that MS disorder progression has an adverse effect on personality and/or behaviour (Benedict et al., 2008). The disorder is furthermore thought to have an impact on cognition on between 43% and 70% of patients (Benedict et al., 2006; Rao, Leo, Bernardin, & Unverzagt, 1991). Functional communication abilities typically are not noticeably affected and cortical dysfunctions such as aphasia and apraxia are rare (Lezak et al., 2012).

2.1.4 Measuring disorder severity

Disorder severity in MS is most commonly measured by means of the Expanded Disability Status Scale (EDSS; Kurtzke, 1983). This measure is derived from neurological examinations which are heavily weighted on ambulation and motor function, although sensory, bowel and bladder, visual and brainstem functions also contribute to the score. The EDSS does not include any neurocognitive psychological examinations, but rather makes use of clinical judgment of "cerebral" functioning. This rating confounds cognitive function and affective state. The EDSS also exhibits certain psychometric limitations which include ordinal scale, poor reproducibility and relative insensitivity to change (Hobart, Freeman, & Thompson, 2000) and is especially insensitive at lower levels of severity (van Winsen, Kragt, Hoogervorst, Polman, & Uitdehaag, 2010).

Alternative measures have been developed in an attempt more accurately to assess and track disorder progression. These measures include the Multiple Sclerosis Functional Composite (Rudick et al., 1997) and the Multiple Sclerosis Severity Score (Roxburgh et al., 2005).

However, despite its limitations the EDSS score is still most commonly used as an outcomes measure in MS clinical trials (Meyer-Moock, Feng, Mauerer, Dippel & Kohlman, 2014).

2.1.5 Disorder course

Two main subtypes of the disorder, based on supposed course of disorder progression, are normally identified at initial diagnosis, viz. relapsing or progressive (Lezak et al., 2012).

Relapsing-remitting Multiple Sclerosis:

Approximately 80% of patients experience a relapse-remitting form of the disorder. Patients typically experience an exacerbation of symptoms over a period of days, followed by either full or partial improvement. This improvement happens either spontaneously or with corticosteroid treatment, over a period of weeks (Noseworthy, Lucchinetti, Rodriguez, & Weinshenker, 2000). Clinical stability is observed between such attacks. Relapsing forms are considered definite MS when at least two distinct attacks have been identified with impacts on at least two distinct regions of the central nervous system (McDonald et al., 2001). An attack (relapse, exacerbation) is defined as "patient-reported symptoms or objectively observed signs typical of an acute inflammatory demyelinating event in the central nervous system, current or historical, with duration of at least 24 hours" (Polman et al., 2011, p. 293). A small-sample study by Foong et al. (1998) indicated a reversal of cognitive impairment as measured during an acute relapse. This recovery is most notable in aspects of attention whilst memory appeared to suffer permanent impairment. In addition their results indicated that recovery is more likely in patients who initially presented with mild (rather than acute) cognitive impairment. The re-assessment of cognition was done approximately six weeks after the relapse.

A subgroup of relapsing-remitting patients is deemed to have Benign MS (Lezak et al., 2012). This group is deemed to have no obvious disease progression with minimal disability

reported decades after onset of the disorder. The definition of this subgroup remains controversial, with the diagnosis currently only based on an EDSS score, which in turn is almost entirely focused on physical disability with a strong emphasis on ambulation (Correale, Ysrraelit, & Fiol, 2012). A combination of a low EDSS score and lengthy disease duration is typically synonymous with Benign MS. Clinicians often view disorder duration of greater than 10 years after onset, during which an EDSS ≤ 3 is maintained, as an indication of Benign MS (see Correale, Peirano, & Romano, 2012). Aspects such as fatigue, depression and cognitive impairment are not taken into account. These factors could be significant in patients with Benign MS and could lead to an overestimation of the prevalence of Benign MS. Indeed, one study reported more than 45% of 163 EDSS-defined Benign MS patients were identified with cognitive dysfunction, fatigue and depression (Rao et al., 1991), which is comparable to statistics in MS patients at large (Amato & Portaccio, 2012). Benedict and Fazekas (2009), in an editorial, also question the utility of using clinical features as the only method of identifying Benign MS. Quoting the consensus opinion of Rovaris et al. (2009), they also suggest the use of cognitive screening to distinguish Benign MS from other disorder courses. This may lead to more patients clearly being diagnosed with Relapsing Remitting MS.

Progressive forms of Multiple Sclerosis:

Progressive forms of MS differ from the Relapsing Remitting form in that there is a progressive course development. Progressive forms are considered definite MS where clinical or MRI evidence provides confirmation of disorder progression over a period of at least one year. This evidence must be supported by laboratory findings (abnormal cerebrospinal fluid and abnormal MRI or visual evoked potentials) with no other plausible neurological cause (Polman et al., 2011).

- Primary Progressive MS

In 20% of patients diagnosed with MS a gradual, nearly continuous course of development is observed from when the first symptoms are identified, and are classified as having Primary Progressive MS. In most instances no clear relapses occur, although in certain instances such relapses may occur superimposed on the normal progressive course of the disorder.

- Secondary Progressive MS

Most patients with an initial Relapsing-Remitting MS diagnosis start progressively deteriorating within 15 years of onset of the disorder, with or without intermittent relapses (Lezak et al., 2012). They are then classified as having Secondary Progressive MS. In certain cases the disorder may develop at a rapid rate. In cases where such development leads to an EDSS score of six within five years, a course is defined as Malignant MS (Gholipour, Healy, Baruch, Weiner, & Chitnis, 2011). This study found that up to 10% of cases could be termed Malignant MS.

It is worthwhile to bear in mind that there is still some disagreement on the classification of the two major forms of MS. As Rodrigues et al. (2011, p. 593) states, there is "not enough evidence to demonstrate that Relapsing-Remitting MS and Primary Progressive MS are in fact distinct disorders. Nevertheless, demographic and clinical data show significant differences between these two courses…" For the purposes of this study, all further references to MS indicate a positive diagnosis of the disorder, with either of the courses of development i.e. Relapsing Remitting or Progressive.

2.1.6 Symptoms and signs before diagnosis

Many individuals diagnosed with MS report experiencing symptoms of the disorder such as fatigue, depression and/or cognitive decline prior to diagnosis, which could indicate a first demyelinating event. Post mortem studies have found some individuals with pathological features of MS who were never diagnosed with MS during their life. This could either indicate that they had an asymptomatic disorder or that the symptoms were of such a low level not to warrant a diagnosis of MS (Spain & Bourdette, 2011). Some individuals have MRI scans consistent with an MS diagnosis, yet have no signs of symptoms. Okuda et al. (2009, p. 801) first suggested the introduction of the classification Radiologically Isolated Syndrome in the MS lexicon, describing the syndrome as "...individuals without overt clinical symptoms but with MRI features highly suggestive of MS."

The vast majority of patients initially present with an isolated clinical symptom. Where such a presentation is done without supporting MRI evidence indicative of MS, a diagnosis of Clinically Isolated Syndrome is given. Approximately 85% of people will initially present with Clinically Isolated Syndrome (Miller et al., 2005). Of these 63% of cases will eventually develop into definite MS (Fisniku et al., 2008). It has furthermore been shown that Clinically Isolated Syndrome individuals with abnormal baseline MRI will develop MS in 82% of cases, whilst only 21% with a normal baseline will do so (Fisniku et al., 2008). It is currently thought that Radiologically Isolated Syndrome leads to Clinically Isolated Syndrome and then eventually to MS (Ramagopalan et al., 2010).

2.2 Cognition in Multiple Sclerosis

2.2.1 Introduction

Although it is generally agreed that MS quite commonly has an impact on cognition, most studies have found that general intelligence is not affected (Macniven et al., 2008). A few researchers have however reported small but significant declines (Rao et al., 1991). MS, as opposed to many other neurological disorders, rarely leads to a diagnosis of dementia. Rather, the impact - which can vary greatly among patients - is generally presented as subtle impairments in one or more specific cognitive domains (Chiaravalloti & DeLuca, 2008). Cognitive decline normally appears to progress gradually over time, generally over a period of a few years (Amato, Zipoli, & Portaccio, 2006). A number of domains have been identified that are affected by MS. Processing speed and visual learning and memory are most commonly affected (51,9% and 54,3% respectively), while areas such as "simple attention" (e.g. repeating digits) and essential verbal skills (e.g. word naming and comprehension) are usually not impacted (Chiaravalloti & DeLuca, 2008). A study of patients with Relapsing-Remitting MS found that almost one in six patients were noticeably impaired, with deficits of at least modest severity in three or more cognitive domains. This incidence increased to between 37% and 49% for impairment in two circumscribed cognitive domains (Fischer, Jacobs, Cookfair, & Rudick, 1998).

2.2.2 Affected domains

2.2.2.1 Information Processing Speed

As the name indicates, the construct of information processing speed is used to describe the speed at which a person can process information (Chiaravalloti & DeLuca, 2008). Reduced

information processing speed is generally considered to be the primary cognitive deficit in patients with MS (DeLuca, Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004; Demaree, DeLuca, Gaudino, & Diamond, 1999; Denney, Lynch, & Parmenter, 2008; Forn, Belenguer, Parcet-Ibars, & Avila, 2008; Macniven et al., 2008; Parmenter, Shucard, & Shucard, 2007; Van Schependom et al., 2014) and is also most often the first cognitive deficit to be evidenced (Van Schependom et al., 2014). Studies have found that patients with MS have significantly slower information processing speed, whilst accuracy of performance remained relatively unchanged (Demaree et al., 1999; de Sonneville et al., 2002; Lazeron, de Sonneville, Scheltens, Polman, & Barkhof, 2006). Lazeron et al. (2006) quote a number of studies which would indicate that cognitive slowing is general, i.e. affects various attentional domains (divided, focused, sustained attention). Research (De Sonneville et al., 2002) found processing speeds of patients with MS to be up to 50% slower than those of healthy controls in attention-demanding tasks, while decreases in automated (implicit) processing tasks registered a decrease of "only" 20% in processing speed compared to healthy controls. Their results confirm the hypothesis that the impact of the disorder on automated processes appears to be less severe.

Denney, Lynch, Parmenter and Horne (2004) evaluated Relapsing-Remitting MS and Primary Progressive MS patients using neurocognitive tests that assessed executive function, verbal learning and memory and speeded information processing. Results indicate that, when the groups were controlled for age, gender, education level, fatigue and depression, the only cognitive measures on which patients differed from controls were those related to speed of information processing. In an eight-year longitudinal study tracking cognitive decline in patients with MS, Bergendal, Fredrikson, and Almkvist (2007) found that the largest decline was in visual reaction time. Compared to auditory response time, visual response time at baseline was

both more impaired at baseline and also showed greater decline over time. Furthermore, this visual response time was shown not to be due to optic neuritis, but is hypothesized to be impacted by the particular neural structures of the visual system.

Information processing speed has been found to be implicated, at least in part, in the deterioration of a number of cognitive domains including attention, working memory, long term memory and executive function (DeLuca et al., 2004; Denney et al., 2008; Denney & Lynch, 2009; Forn et al., 2008; Janculjak, Mubrin, Brinar, & Spilich, 2002; Macniven et al., 2008). The possible impact of processing speed on task performance should therefore be taken into consideration when interpreting any time-dependent assessments of higher order cognition (Macniven et al., 2008). Research has found that age is the one covariate factor that is significant when analysing measures of processing speed. Given the fact that it is well known that aging leads to a general decline in information processing speed it may be stated that MS appears to contribute to an exacerbation of normal age-related declines in information processing speed (Denney et al., 2008).

2.2.2.2 Attention

There are a number of widely varying definitions of attention. Lezak et al. (2012, p. 36) citing Parasuraman states that "Attention refers to capacities or processes of how the organism becomes receptive to stimuli and how it may begin processing information or attended-to excitation (whether internal or external)". Attention is deemed to have finite resources and have the capacities both for disengagement in order to shift focus and for responsivity to sensory or somatic stimulus characteristics. Attentional capacity, besides varying between individuals, also varies within individuals at different times and under different conditions (Lezak et al., 2012). Research on specific aspects of attention often provide conflicting results, possibly due to the

varying definitions used to describe attention and qualitatively different instruments used to measure such aspects. Information processing speed or executive control could often be the primary aspect measured in an assessment labelled as "attention" by an investigator (Chiaravalloti & DeLuca, 2008). Benedict and Zivadinov (2011) point out that a challenge when assessing attention is that it is in fact difficult to operationally separate the constructs of processing speed and attention. The impact of fatigue on assessments of attention is furthermore often not taken into account (Chiaravalloti & DeLuca, 2008). Bearing the above cautionary notes in mind, the following broad inferences are made on research on attention deficits in MS.

Basic attention tasks, i.e. tasks that can be done without concentrated mental effort and only require automated processing, is normal in most patients with MS (Paul, Beatty, Schneider, Blanco, & Hames, 1998; Rao et al., 1991) although some dysfunction, especially in auditory tasks, has been reported (Beatty, Paul, & Wilbanks, 1995). Selective attention performance varies in patients with MS. It is dependent on task demands and disorder factors (Lezak et al., 2012). Tests using auditory verbal stimuli (as opposed to visual stimuli) tend to highlight apparent deficits (Foong et al., 1997). Increased disorder activity may lead to a greater compromise in attentional resources, resulting in performance impairment on even less demanding selective attention tests (Grigsby, Ayarbe, Kravcisin & Busenbark, 1994). Divided and alternating attention is almost always impacted by MS. This is immediately apparent in tasks requiring that attention be shifted back and forth from one stimulus to another or where two operations need to be executed simultaneously (Grigsby et al., 1994.; see also Beatty et al., 1995). A bimodal study (auditory and visual tasks) of both selective and divided attention found that divided attention was more severely impacted. The authors however caution that the role of

working memory when considering these impacts needs further investigation (McCarthy, Beaumont, Thompson, & Peacock, 2005).

One study which attempted to address the problem of separating the impact of processing speed from attention was done by Urbanek et al. (2010). This study based their thesis on the work of Posner and Petersen's (1990) proposed model of attention which included three separate aspects, namely functions of alerting (achieving and maintaining a state of alertness), orienting (selection of information from sensory input) and executive control (resolving conflict among responses). Subsequent brain scanning studies have indeed shown that separate brain regions could be associated with each of these aspects of attention (Fan, McCandliss, & Sommer, 2002). Urbanek et al. (2010) used the Attentional Network Test, a computerised test that has been shown to measure each of these attentional networks with moderate reliability, to investigate attention in patients with Relapsing-Remitting MS. Results indicate no significant difference between patients and healthy controls in the orienting and executive functions of attention. However, patients significantly underperformed healthy controls on the alerting functions. Interestingly, these alerting deficits could not explained by overall cognitive slowing.

2.2.2.3 Memory and learning

MS appears to impact on all of the various types of memory (working, short-term and long-term memory) albeit to varying degrees (Staffen et al., 2002; Thornton & Raz, 1997). Implicit memory in general remains mostly unaffected (Rao et al., 1993). In contrast, explicit memory is one of the most commonly impacted cognitive domains of the disorder (Prakash, Snook, Lewis, Motl, & Kramer, 2008). Semantic memory is normally fairly well preserved (Rao et al., 1993). This is also true in terms of individual-specific memory where personal semantic information is not as affected as episodic autobiographical memory (Kenealy, Beaumont,

Lintern, & Murrell, 2002). Episodic autobiographical memory is furthermore also suggested to be particularly sensitive to MS related neuropathology (Ernst et al., 2013). More intact autobiographical memory has been found to be correlated with a greater reduction in quality of life. This may be due to the fact that the patient is more able to compare his present condition with his premorbid functioning and is aware of the deterioration of his condition (Kenealy et al., 2002). Prospective memory i.e. patients' failure to perform future actions, has often been found to be impaired in patients with MS (Bravin & Kinsella, 2000; Rendell et al., 2012).

There are great inconsistencies found between studies reporting on memory performance of patients with MS. This may in part be due to the fact that MS is such a heterogonous disorder, with disorder subtype impacting on results (Wachowius, Talley, Silver, Heinze, & Sailer, 2005). In a study of memory performance of patients with MS and healthy controls (Beatty et al., 1996) the following patterns were observed: 24% - 36% of patients performed on a level similar to that of the healthy controls, with essentially intact learning and recall. The most common pattern (43% to 56% of patients) was what was termed "inefficient" performance. Overall these patients' performance was similar to that of the healthy controls; however detailed analysis indicated deficient first trial recall, mildly inconsistent recall across trails, and mildly deficient delayed recall. The remainder of the patients was found to be significantly impaired in various aspects of memory and learning, including a flatter learning curve, extremely poor delayed recall and numerous intrusion errors.

Studies of the impact of MS on memory have generally focused on two main areas namely acquisition and retrieval (Chiaravalloti & DeLuca, 2008). Results from a number of studies indicate that acquisition, rather than retrieval, is the core deficit in memory impairments of patients with MS (DeLuca & Gaudino, 1998; Demaree & Gaudino, 2000; Lafosse, Mitchell,

Corboy, & Filley, 2013; Minden, Moes, Orav, Kaplan, & Reich, 1990; Thornton, Raz, & Tucker, 2002). It is significant to note that DeLuca et al. (1998) found that whereas both verbal and visual memory impairment is due to acquisition, visual memory decline was furthermore also associated with impaired storage. Declines in acquisition/new learning in MS can to a large degree be explained when considering the impact of deficits in processing speed (DeLuca et al., 2004; Demaree et al., 1999, Lafosse et al., 2013). In a recent study (Chiaravalloti, Stojanovic-Radic, & DeLuca, 2013) the relative impact of processing speed and working memory on new learning was assessed in patients with MS. Results indicate that variance in new learning is primarily related to processing speed deficits whilst deficits in working memory had a relatively small impact. Prospective memory impairment has furthermore also been strongly linked to patients' inability to capture the content of intended future tasks due to impaired processing speed, rather than failure to remember to do the actual task at some point in the future (Bravin & Kinsella, 2000).

2.2.2.4 Language

The impact of MS on language is still not clear (Barwood & Murdoch, 2013). Syndromes such as aphasia and alexia are extremely rare (Jonsdottir, Magnússon, & Kjartansson, 1998; Lacour et al., 2004). When they do occur, it is typically during a relapse. These syndromes mostly resolve again after corticosteroid treatment of the relapse (Lezak et al., 2012). In the past it has generally been thought that language abilities of patients with MS do not differ substantially from healthy controls, however a comprehensive study by Murdoch and Lethlean (cited in Mackenzie & Green, 2009) found that whereas more than 50% of the sample did indeed have essentially normal language abilities, the remainder presented problems ranging from naming, word definition, word fluency, sentence repetition, verbal explanation, verbal reasoning

and higher-level comprehension. Kujala, Portin, and Ruutiainen (1996) proposed that impacts in language were cognitively related; patients with preserved cognitive abilities did not present with any language deficits, whilst certain language functions showed impact even when associated with mild cognitive decline. In a study which evaluated both high- and low-level language abilities in patients with MS, Barwood and Murdoch (2013) found that tests evaluating high-level abilities (e.g. draw conclusions, form complex sentences, interpret abstract semantic meaning and repeat information) were more impaired in comparison to healthy controls, than low-level abilities (e.g. those requiring less interpretation of complex and abstract linguistic structures, and more common language tasks).

A number of studies of patients with MS have found that verbal fluency is often impaired (Henry & Beatty, 2006; Zakzanis, 2000). The study by Henry and Beatty (2006) found that reduced processing speed, rather than impaired executive functioning, to be the primary cause underlying this reduction in verbal fluency. Furthermore, their quantitative review of 35 studies found that phonemic and semantic fluency impairment was of a comparable level, indicating that semantic memory as such is most likely not impaired.

2.2.2.5 Visuoperceptual Ability

MS often affects the sensory aspects of the visual system of patients. In addition disorders of visuoperception are also often a result of MS (Rao et al., 1991). Vleugels et al. (2000), using an extensive battery of neurocognitive tasks evaluating both spatial and non-spatial aspects of behaviour, estimated a prevalence of visuoperceptual impairment of at least 26% in the general MS population. Their study furthermore highlighted the fact that such visuoperceptual impacts on patients with MS are very diverse and cannot be deemed a unitary syndrome.

Visuospatial perception has been shown to be negatively impacted by MS (Rao et al., 1991). In their study of how the disorder impacts on spatial working memory, Gmeindl and Courtney (2012) confirmed that it is often impaired. Their study found that whereas visuomotor speed of processing was impacted, this factor alone could not explain the impairment of Working Memory. Furthermore, their study indicated that, for patients with MS, slowed voluntary reorientation of attention is strongly correlated with poor encoding of spatial locations into working memory. Further research is however required to confirm whether this correlation can in fact be deemed to be causal. One commonly used test in the evaluation of MS patients' visuospatial abilities is the Brief Visuospatial Memory Test - Revised (Benedict et al., 2002). A recent study indicated that processing speed is a major contributor to both learning and memory results of this test and the authors suggested that the impact of slowed processing speed must be considered when interpreting results (Tam & Schmitter-Edgecombe, 2013).

Non-spatial visual perception was investigated using a stage model of object recognition (Laatu, Revonsuo, Hämäläinen, Ojanen, & Ruutiainen, 2001). This revealed that patients had problems at both the early stages of the visual feature processing (as indicated by slowed reaction times) and later semantic categorization and identification stages (as indicated by higher error rates). Their study furthermore suggests that early stage shape recognition problems are independent of underlying sensory and motor dysfunction. In addition the study also once again underlines the importance of speed of processing on the various aspects of cognition affected by MS.

2.2.2.6 Executive functions

Executive functions include aspects required for complex, goal-directed actions, as well as the ability to adapt to environmental change or demands. It includes the ability to plan,

anticipate outcomes and to direct resources appropriately (Lezak et al., 2012). Rao et al. (1991) estimated that approximately 19% of patients with MS suffer from impairment in this cognitive domain. Another comprehensive study of various aspects of executive functioning in patients with MS (Drew, Tippett, Starkey, & Isler, 2008), found that the majority of patients had impairments in some aspects of executive functioning, while 17% of patients had below average performance on more than five measures. A longitudinal study found significant deterioration in decision-making of patients with MS over a two year period (Simioni et al., 2009).

It should again be noted that speed of processing could have a major impact on assessments of executive functioning. Verbal fluency tasks have consistently been shown to be more sensitive in the assessment of impairments in MS than other executive function tasks (Crawford & Henry cited in Henry & Beatty, 2006). However, Henry and Beatty (2006) also make the point that in MS compromised information processing speed, rather than executive functioning, may be a primary contributor to deficits in verbal fluency task performance. In the same way, Drew et al. (2008) also caution that they used two shifting and inhibition tasks which were time related, and that processing speed impairments could have a major impact on results.

2.2.2.7 Social cognition

It has long been known that MS has a negative impact on a patient's social life, including partnership roles, family roles and employment (Halper, 2007). Social cognition, the foundation of successful social functioning, consists of the ability to perceive and interpret socially relevant stimuli, and to provide an appropriate response to them. Theory of Mind, a crucial component of social cognition, involves the ability to attribute mental states to one's self or others and hence predict or understand possible behaviour. Banati et al. (2010), in a comparative study of ambulatory mild to moderately impaired (EDSS $\leq$ 4,5) Relapsing-Remitting MS patients found

that Theory of Mind abilities were negatively impacted even in the absence of any indication of declines in general intelligence measures. This impact of MS on declines in Theory of Mind, after controlling for confounding factors such as fatigue and depression, were found to be significant. It is important to note here that MS related cognitive impairment per se, and not MS as a disorder in general, was found to contribute to a reduction in Theory of Mind performance (Benedict et al., 2002). A study by Pöttgen, Dziobek, Reh, Heesen, and Gold (2013) confirmed impaired Theory of Mind abilities in patients with MS, and furthermore indicated that such impairments were not simply a result of other neuropsychological deficits (e.g. depression and cognitive impairment).

Further proof of declines of social cognitive abilities is provided by a study which looked at the impact of MS on affective prosody (Kraemer et al., 2013). Prosody, a component of social cognition, refers to the non-linguistic aspect of language and is characterized by acoustic features such as timing, intonation, rhythm, stress and differential pausing. Affective prosody in turn refers to the emotional tone of language. This takes precedence when the emotional tone and semantic content of a verbal message are not consistent. In their study, Kraemer et al. (2013) found that affective prosody impairments were present in the early stage of the disorder in young patients. They suggest that, when developing a treatment regime for patients, both overt physical impairments and invisible symptoms should be taken into account. Both Banati et al. (2010) and Kraemer et al. (2013) propose that social cognition, which requires considerable cognitive resource inputs, could contribute to a decrease in concentration and fatigue.

2.2.3 Factors affecting cognitive performance in patients with MS

As indicated above, cognitive functioning suffers in most patients with MS. There are no absolute predictors of which patients will be affected, however a number of factors have been identified that are deemed to have an impact on cognitive performance.

2.2.3.1 Age

It is well-known that older age is related to declines in cognitive performance, and in particular to speed of processing (Lezak et al., 2012; Salthouse, 1996). Specifically with respect to MS, in one cross-sectional study of patients with MS matched with healthy controls it was found that the effect of aging, as measured by the speeded Stroop test, was of similar magnitude (Bodling, 2010). A study by Till et al. (2011) investigated patients who were younger than 18 years old at the time of their first MS attack. Results indicated that such early onset appears to be related to more severe cognitive decline. The authors speculate that this might be due to the fact that plasticity of the paediatric brain is not sufficiently developed at the time of onset to provide a possible buffer to the impact of the disorder on their cognitive neural networks.

2.2.3.2 Race

A number of MS studies have indicated a more aggressive disorder course for non-Caucasian than for Caucasian individuals (Weinstock-Guttman et al., 2003; West, Wyatt, High, Bostrom, & Waubant, 2006). This in itself does not however necessarily indicate increased risk for cognitive decline. Although at least one review study found that African-American patients did perform more poorly than their Caucasian counterparts on cognitive measures (Wishart & Sharpe, 1997), more recent research indicates that such differences are not statistically significant after controlling for effects of socioeconomic status (Marrie, Cutter, Tyry, Vollmer, & Campagnolo, 2006).

2.2.3.3 Gender

Whereas MS is much more prevalent in females than in males (see section 2.1.1 above), studies have indicated that male patients suffer more from cognitive decline than women, both in terms of severity and incidence (Beatty & Aupperle, 2002; Savettieri et al., 2004).

2.2.3.4 Cognitive Reserve

Various MRI studies using patients with MS have investigated the impact of implicated brain abnormalities, particularly of regional and whole brain atrophy. Findings indicate that atrophy only accounts for approximately a third of the variance in neurocognitive performance in the subjects.

The question that must therefore be asked is why cognitive deficits are not consistently more severe in patients with MS and why these deficits are not more closely correlated with observed brain atrophy. One possible contributing factor is the impact of Cognitive Reserve. Cognitive Reserve describes the concept that the brain can respond to insult by either behavioural adaption or neurocognitive compensation, possibly by activation of existing or alternate neural pathways (Benedict, Morrow, Weinstock Guttman, Cookfair, & Schretlen, 2010). Cognitive Reserve is thought to be composed of two components: passive reserve reflects past and premorbid indicators of brain reserve (e.g. IQ, educational attainment) whilst active reserve refers to current activity. A number of studies in the past have focused on the role of passive Cognitive Reserve in buffering the impact of neurodegenerative diseases. Benedict et al. (2010) found that passive Cognitive Reserve, as indexed by either higher premorbid intelligence or more years of education, is shown to protect against cognitive decline in MS. Whilst not measuring cognitive performance per se, a recent longitudinal study of passive and active Cognitive Reserve in MS found that passive Cognitive Reserve had no effect on disability

progression. Rather the authors suggest that active Cognitive Reserve acts as a strong buffer against progression of neurologic disability (Schwartz, Quaranto, Healy, Benedict, & Vollmer, 2013). They do however caution that further research is needed to establish causality of active Cognitive Reserve on disability progression.

2.2.3.5 Genetics

Apolipoprotein E (APOE) has been well studied in terms of its impact on human cognition. This is also true in terms of MS, where a number of studies have specifically focused on the possible role of the ε4 allele. In their review of studies that focus on the impact of the APOE ε4 gene on cognitive dysfunction in MS, Ghaffar and Feinstein (2010) came to the conclusion that it would appear as though this genetic factor may play a role in the impact of MS on cognition. Their review of five studies on this topic found that ε4+ patients exhibit greater cognitive decline and possibly more brain atrophy than their ε4- counterparts. The authors do however caution that limitations in the research to date make these conclusions only tentative at this stage.

2.2.3.6 Smoking

Several meta-analyses (D'hooghe, Nagels, Bissay, & De Keyser, 2010; Handel et al., 2011; Hawkes, 2007; Wingerchuk, 2012) have highlighted the negative impact of smoking on patients with MS. These negative impacts include the association between smoking and the subsequent development of MS (see also Salzer et al., 2013) and an association with higher lesion volume and atrophy, whilst contradictory results were found regarding the impact of smoking on disorder progression. One small-scale study which specifically looked at the possible role of smoking in patients with signs of severely impaired cognitive abilities found an overrepresentation of smokers, indicating that this modifiable factor may lead to increased

cognitive impairment (Staff, Lucchinetti, & Keegan, 2009). Research has also indicated that smoking reduces the micro-structural integrity of white matter and is associated with impaired cognitive performance (Gons et al., 2011). Interestingly, the authors are of the opinion that the cessation of smoking may reverse the impaired structural integrity.

2.2.3.7 Disorder course

Disorder course appears to be related to severity of cognitive impairment. Although the subtype classifications of disorder course are primarily based on physical changes as noted by neurological exams they do have some, albeit very limited, predictive value in terms of cognitive dysfunction. Progressive subtype patients are more prone to cognitive dysfunction than Relapsing-Remitting MS (Huijbregts et al., 2004; Rodrigues et al., 2011; Thornton & Raz, 1997), although at least one review study (Wishart & Sharpe, 1997) found very little relationship between subtype and cognitive status. Of the progressive forms Secondary Progressive MS has been found to be more susceptible to cognitive impact than Primary Progressive MS (Comi et al., 1995; Huijbregts et al., 2004). A small-sample study by Foong et al. (2000) found that differences between Secondary Progressive MS and Primary Progressive MS are however much less pronounced when patients are equated for disorder duration and disability.

A comparative study of the prevalence of cognitive impairment in the various MS subtypes indicated that cognitive impairment is found in all of the stages and subtypes. The prevalence rates reported were as follows: 27,3% in Clinically Isolated Syndrome, 40,0% in Relapsing-Remitting MS, 56,5% in Primary Progressive MS, and 82,8% in Secondary Progressive MS (Potagas et al., 2008), while Benign MS has a reported cognitive impairment rate of 45% (Rao et al., 1991). Despite all the above instances it is important to note that disorder course alone cannot predict cognitive status of individual patients (Lezak et al., 2012).

2.2.3.8 Disorder duration

A number of short-term studies have found only a weak correlation between cognitive function and disorder duration, whilst long-term studies show conflicting results (Sartori & Edan, 2006). This is not surprising as cognitive atrophy can occur early in the disorder, contributing to the weak relationship between cognitive ability and disorder duration. Furthermore, in cases where lesions are primarily in the spinal column resulting in major physical disability, it is possible that cognitive function may still remain intact.

2.2.3.9 Depression

In a review of research on depression in MS, Siegert and Abernethy (2005) found that depression is quite common in MS. Their review indicates that a lifetime occurrence of 50% of depression is commonly reported. This level of depression is elevated when compared to both the general population and to other chronic conditions. For example, the American general population lifetime prevalence is estimated at 10-15% (American Psychiatric Association, 1994). Regarding possible causative factors it is interesting to note that the onset of depression is rarely before MS symptoms ensue (Minden, Orav, & Reich, 1987) and is not linked to family history (Sadovnick et al., 1996), but rather to disorder-related changes themselves such as increased lesion load and brain atrophy as well as immunological complications, all of which have been shown to be associated with depression (Arnett, Barwick, & Beeney, 2008). Patients with MS furthermore display significant inter-individual variance in levels of depression. Arnett et al. (2008) make the point that this great variance is probably due to the result of the interaction of common MS sequelae (physical disability, cognitive dysfunction and pain) and possible moderating factors (social support, methods of coping, levels of stress and conceptions of self and illness).

A number of studies have been done to investigate the impact of depression on cognitive functioning in patients with MS. Results are equivocal. The review study by Arnett et al. (2008) found research which did indicate a relationship between depression and cognitive performance (e.g. Arnett, Higginson & Randolph; Denney et al. and Landro, Celius & Sletvold) as well as studies without any clear relationship (e.g. Minden et al.; Rao et al., 1991; and DeLuca, Barbieri-Berger & Johnson). Arnett et al. (2008) did however make the important point that studies with large enough sample sizes tend to indicate a relationship. Other research has also produced confounding results. (Demaree, Gaudino, & DeLuca, 2003) found that cognitive deficits in patients with MS only became significant at higher levels of depression. In an interesting longitudinal study Kinsinger, Lattie, and Mohr (2010) evaluated MS patients with an initial high level of depression. They could not find any evidence that depression contributed to cognitive decline in MS. A large-sample study using three different sample sets of MS patients, all measured to be in the mild to moderate depressive range, could also not find any correlation between depression and cognitive performance (Allen, 2011). More recent work (Gmeindl & Courtney, 2012) indicated that whereas mild depression could account for some degree of impairments in memory span in both patients with MS and healthy controls, it could not reliably be shown to specifically explain working memory deficits in patients with MS.

2.3 Assessing cognition in MS

2.3.1 The role of neurocognitive assessments in MS

The accurate detection of cognitive decline in MS is often quite a challenge. MS most often results in focal rather than global cognitive deficits, may be very subtle, and typically varies between patients. As a result interviews or neurological examinations, even by a skilled examiner, often fail to detect such subtle cognitive impacts of the disorder (Benedict et al.,

2002). Furthermore, a survey amongst neurologists revealed the assumption that there is a strong correlation between physical disability and cognitive impairment; this despite several published studies to the contrary (Fisher et al. cited in Sartori & Edan, 2006). This may partially explain why cognitive deficits in patients with little or no physical handicaps are often overlooked during neurological examinations (Sartori & Edan, 2006).

Cognitive deficits often occur early in the course of the disorder, frequently prior to final MS diagnosis (Sartori & Edan, 2006). Furthermore, although relatively rare, cognitive decline may also in certain cases be the presenting problem (Etgen, Adler-Hunklinger, & Hemmer, 2012). At the general population level, Bergendal et al. (2007) in their longitudinal study of cognitive decline, found baseline measures of information processing a strong predictor of long-term cognitive decline. This supports findings by Kujala, Portin, and Ruutiainen (1997) who furthermore found that other disorder variables could not predict cognitive decline. In a review of neurocognitive aspects of MS, Wishart and Sharpe (1997, p. 811) state that the "accurate detection of cognitive impairment in patients with MS has important ramifications for social and occupational functioning."

As part of the treatment and rehabilitation of the disorder, earliest detection of cognitive impairment is considered to be of particular importance (Benedict et al., 2002). Cognitive rehabilitation of patients with MS appears to be more successful in cases focusing on specific areas of cognitive dysfunction as opposed to those programs addressing diverse cognitive deficits (Glanz et al., 2010). There is therefore a clear need to identify and understand those areas of cognition impacted by the disorder. The impact of the disorder on cognition is an aspect which could stage progression of the disorder, independent of physical abilities (Sartori & Edan, 2006). Tracking of disorder progression by monitoring cognitive abilities could be especially important

in the early phases of the disorder, as it presents a more stable measure than the often remitting physical symptoms (Winkelmann, Engel, Apel, & Zettl, 2007). This tracking could also be an important aspect in the monitoring and implementation of any therapeutic intervention for patients with MS.

From the above it is clear that the early and ongoing accurate identification and tracking of cognitive performance in patients with MS by means of neurocognitive assessments is of critical importance.

2.3.2 Challenges in the neurocognitive assessment of patients with MS

There are a number of challenges when assessing and interpreting the cognitive performance of patients with MS.

2.3.2.1 Sensory and motor impairments

The possible impact of sensory and motor impairments on test results must be considered when assessing the cognitive abilities of patients with MS. For example, in cases where a speeded test requires a spoken response, dysarthria has been shown to negatively impact the test performance (Smith & Arnett, 2007). MS patients commonly experience visual disturbances. These disturbances can be quite varied and can include blurred vision, double vision resulting from incoordination of the eyes, and partial loss of vision in one or both eyes, loss of colour perception, blindness in one or both eyes, and impaired ability to process individual features of visual stimuli and eye movement abnormalities. It is estimated that at least two-thirds of MS patients suffer from one or two of these visual impairments at some point in their illness. Visual memory tests which require drawing should be avoided. As an alternative it is suggested that visual recognition tests should be used. Auditory dysfunction is less common, although hearing loss in one or both ears is often experienced in cases of brainstem lesions (Lezak et al., 2012).

MS often leads to motor symptoms, with between 80% and 90% of patients reporting episodic or persistent limb weakness, spasticity and/or incoordination. Combinations of these symptoms are the norm. Lezak et al. (2012, p. 296) make the point that: "Since MS patients inevitably perform poorly on tests requiring fine sensory discrimination or rapid coordinated motor responses, test batteries should minimize sensory and motor demands." Where such demands are thus foreseen, it would be important to control for such possible impacts. This would for example be the case for computerised assessments which are mouse-driven. One way of measuring and controlling for the possible impact of the disorder on the speed of utilising a computer-mouse is the finger tapping test. Significant motor deficits as measured by finger tapping tests have been found in patients with MS (Heaton, Nelson, Thompson, Burks, & Franklin, 1985; Stoquart-Elsankari, Bottin, Roussel-Pieronne, & Godefroy, 2010; Zeller et al., 2010). One small-sample study (Stoquart-Elsankari et al., 2010) concluded that simple response time as measured by a finger tapping test was due to subtle motor deficits and not caused by either perceptual or cognitive deficits. This would indicate that the impact of such motor deficits should be controlled for when assessing patients with MS. There are many variations of the finger tapping test. A simple test requiring minimal specialised equipment was developed by Worthington and De Souza (1989). Their study found that this test was a consistent and objective method when measuring the speed of the index finger tapping in patients with MS.

2.3.2.2 Fatigue

Fatigue is one of the most common and debilitating features of MS. Research (Krupp et al., 1995) indicates that between 76% and 92% of patients with MS complain of fatigue and that it has an effect on their quality of life. Fatigue is relatively independent of factors such as the duration of the disorder and physical disability. It is thought to result from a combination of

factors such as impaired nerve conduction, depression and anxiety, physical disability and cognitive impairment. Central factors thought to further contribute to fatigue include metabolic abnormalities of the frontal cortex and basal ganglia, increased cortical activity during movement and immune dysfunction (Lezak et al., 2012). In addition, energy production by mitochondria requires specific nutrients such as iron and vitamin B12, which are often deficient in people with MS (van Rensburg et al., 2006; van Rensburg, Kotze & van Toorn, 2012).

Fatigue is often cited by patients as having a significant impact on their cognitive functioning. However, it does not appear to directly impact objectively measured cognitive performance (Bol, Duits, & Hupperts, 2010; Kinsinger et al., 2010; Morrow, Weinstock-Guttman, Munschauer, Hojnacki, & Benedict, 2009). It should be noted that, as Bryant, Chiaravalloti, and DeLuca (2004) caution, cognitive fatigue in patients with MS may impact performance in situations where sustained cognitive performance is required. This should be taken into consideration when designing or selecting a test battery for patients with MS.

2.3.2.3 Pain

A further physical symptom of MS that could impact on cognitive performance is pain. Pain is generally accepted to be a common symptom of MS; however estimates of its occurrence vary widely. In an attempt to get a more accurate estimate of the prevalence of pain in MS, Kerns, Kassirer, and Otis (2002) reviewed a number of studies. Their conclusion was that an estimated prevalence of at least 50% is a realistic figure. A study by Svendsen and Jensen (2003) did not find a significant difference between pain prevalence in MS subjects compared to a background sample. However, the patients with MS did report a significantly greater intensity of pain. The possible impact of pain on cognitive performance is not clear. Research on cognitive performance in the presence of pain is complicated by symptoms often associated with

such pain e.g. anxiety, depression and emotional distress. The presence of such symptoms may in itself impact on cognitive performance. (Lezak et al., 2012). At the very least the possible impact of pain should be minimized by ensuring that the physical aspects of the assessment are adjusted to ensure optimal comfort for the patient.

2.3.2.4 Heat

Some MS patients are very sensitive to heat, whether external (e.g. ambient temperature in a room) or internal body heat such as fever or elevated body temperature due to physical exertion. Heat worsens existing symptoms and may even bring on new symptoms (Lezak et al., 2012). A reduction in body temperature fortunately normally leads to a return to baseline levels of MS symptoms. The impact of heat must be taken into consideration when choosing the time and place for assessments.

2.3.2.5 Medications

It is known that certain MS medications can affect cognitive performance. Langdon et al. (2012) noted research that implicates the following medications as having a negative effect: benzodiazepines, high doses of anti-spasticity agents such as baclofen, anticonvulsants, antidepressants and cannabis. On the other hand, a number of large randomized clinical trials of the last two decades have consistently shown that disorder-modifying treatments such as interferon-β and glatiramer acetate reduce relapse rates and the development of new MRI lesions and, in some cases, even modify short-term disability. Based on these trials a number of disorder-modifying treatments have been approved for use in relapsing forms of MS, but not for use in primary progressive forms of the disorder (Lezak et al., 2012). None of the medications are registered for prevention of disability progession. The impact of these treatments on cognition remains largely unclear. Research using the drug donepezil (Krupp et al., 2011) found

no improvement on memory, whilst a two-year study by Fischer et al. (2000) did note limited beneficial impact of interferon-β in patients with Relapsing-Remitting MS.

2.4 Neurocognitive assessment tools in MS

2.4.1 Background

Neurocognitive assessments in MS are on a continuum from brief single screening tests which are done in order to identify patients requiring further testing, to comprehensive assessments of a patient's cognitive strengths and deficits. Routine neurocognitive testing takes an intermediate approach, and normally consists of a battery of tests that attempts to assess those cognitive functions most commonly found to be impaired by MS (Benedict et al., 2002). Assessment tools are traditionally done with paper and pencil. However, there has been an ever-increasing development of computerised tests in recent years.

2.4.2 Paper and Pencil Single test screening

Cognitive impairment in patients with MS is often difficult to detect during routine neurological examinations. Brief single test screenings for cognitive impairment is therefore often utilized to indicate patients who may require further more complete neurocognitive assessment. The Symbol Digit Modalities Test (SDMT; Smith, 1982) is one of the most commonly used of such screening tests. It is an easy to administer paper-and-pencil test which is user-friendly and only takes a few minutes to complete with minimal use of equipment. The test consists of a stimulus page containing nine symbols, each paired with a single digit. The remainder of the page consists of a pseudo-randomized sequence of the symbols. Participants are required to match the symbols with its paired digit, attempting to correctly match as many as possible symbols within a timed period of 90s. Research indicates that the SDMT may be

effectively applied as a screening test for MS-related cognitive impairment (Parmenter, Weinstock-Guttman, Garg, Munschauer, & Benedict, 2007). The SDMT is believed to measure information processing speed, visual working memory and concentration, primarily by assessing visual scanning and tracking (Spreen & Strauss cited in Iverson, Lovell, & Collins, 2005).

Another commonly used single test screening tool is the Paced Auditory Serial Addition Test (Gronwall, 1977). There are a number of ways in which this test may be administered. The most common way of administration, involves the presentation of an auditory recording of a sequence of paired numbers read out at a particular speed. The respondent is then required to add the presented pair of digits and then to say the answer out loud. The following number on the recording must then be added to this previously presented number (not to the previously calculated sum of numbers), i.e. the third number is added to the second number, the fourth number is added to the third number and so on. After each addition, the answer must be stated out loud. The test therefore requires a person to keep one number in working memory while performing a mathematical operation (addition). This is done at various speeds of number presentation. The scores may be the individual number of correct answers at each speed of presentation, or the overall number of correct answers achieved for all of the different speeds of presentation.

There are a number of distinct advantages to using the SDMT rather than the Paced Auditory Serial Addition Test. The Paced Auditory Serial Addition Test is often associated with psychological stress and agitation and is not well received by patients, with a high percentage of drop outs reported. This test furthermore assumes a certain level of mathematical ability that influences task performance and is also more susceptible to practice effects than SDMT (Sonder, Burggraaff, Knol, Polman, & Uitdehaag, 2014). Whereas the Paced Auditory Serial Addition

Test and SDMT appear to have similar degrees of reliability, SDMT is indicated to have a greater sensitivity in correctly discriminating cognitively impaired patients from preserved patients (Benedict et al., 2006; Drake et al., 2010). In the development of their proposed new neurocognitive assessment battery for patients with MS, Langdon et al. (2012) recommended the inclusion of SDMT (oral form) ahead of the Paced Auditory Serial Addition Test, based both on SDMT's better psychometric characteristics and ease of administration. A recent long-term study (Sonder et al., 2014) compared both the Paced Auditory Serial Addition Test and the SDMT to the Brief-Repeatable-Battery of Neuropsychological test's global cognition scores. Results indicate that SDMT was more highly correlated to the Brief-Repeatable-Battery of Neuropsychological test and it was concluded that compared to the Paced Auditory Serial Addition Test it is more valid and reliable as a single assessment tool for cognition in MS.

2.4.3 Paper and Pencil Incidental learning tests

Incidental learning is commonly described as learning that takes place without any intent to learn. Lezak et al. (2012) point out that as incidental learning reflects what happens in real-world situations, it is often a worthwhile test to administer. A distinguishing characteristic of this type of learning is that it is considered to be an automatic process and consequently requires little cognitive capacity (Hartlage, Alloy, Vazquez, & Dykman, 1993). Assessing for incidental learning is often done as an addition to a test battery where recall of aspects of a particular subtest are requested without priming the participant for such recall. Subtests commonly utilized for this type of assessment include the Wechsler Adult Inventory Scale - Revised (WAIS-R) Digit Symbol subtest, the WAIS Similarities Test, the SDMT and the Boston Naming Test (Lezak et al., 2012).

Brain disorders are however not often assessed using incidental learning tests (Demakis, Sawyer, Fritz, & Sweet, 2001; Lezak et al., 2012). Results from research on Parkinson's Disease using incidental learning tasks are contradictory. One study using an auditory incidental learning task found impaired performance in non-demented patients with Parkinson's disease (Ivory, Knight, Longmore, & Caradoc-Davies, 1999). However, a later study using a word recall incidental learning task (Azuma et al., 2000) considered both demented and non-demented Parkinson's patients. Their results indicated impairment in the demented but not in the non-demented group. A study comparing performance of Parkinson's and Alzheimer's patients found that, whereas patients performed comparably on the normal WAIS-R Digit Symbol test, the associated incidental recall test performance of Alzheimer's patients was significantly worse than the Parkinson's group (Demakis et al., 2001). A study was done comparing groups with either dementia or depression and in a healthy control group using both an incidental learning test and the Logical Memory and Visual Reproduction tests of the Wechsler Memory Scale. Although no formal statistical analyses were done results would appear to indicate that of the three tests Digit Symbol Incidental Learning was the most accurate in discriminating between the demented and the depressed groups. The demented group performed much worse than the depressed group on the incidental test, whilst their performance on the Wechsler memory tests was comparable (Hart, Kwentus, Wade, & Hame, 1987).

Performance on incidental recall in patients with MS has also received some attention. Studies utilising verbal incidental recall tasks have indicated no significant difference between patients and healthy controls (Andrade & Bueno, 1999; Coolidge, Middleton, Griego, & Schmidt, 1996). However, a study using an adapted SDMT Immediate Recall test found that patients with MS performed significantly worse than healthy controls (Minden et al., 1990). An

interesting finding of the study by Coolidge et al. (1996) was that verbal memory tests which included an interference component resulted in significantly worse performance in patients than in the healthy control group. Research has indicated that automatic processing does not appear to be affected by depression (Šoštarič & Zalar, 2011). Therefore, testing for incidental recall (considered to be an automatic process) may provide results that limit the impact of depression.

2.4.4 Paper and Pencil Screening Batteries

To facilitate an intermediate type of assessment, various batteries of tests have been developed. A number of screening batteries, with varying sensitivity and specificity, are used to measure cognitive function in patients with MS (Scherer, 2007). Screening batteries developed for patients with MS perform quite well, with Sartori and Edan (2006) reporting sensitivities ranging from 71% - 100% and specificities between 80 – 94% for four of the most commonly used batteries. The 45-minute Brief-Repeatable-Battery of Neuropsychological tests (Rao, 1990) and the 90-minute Minimal Assessment of Cognitive Function in Multiple Sclerosis (Benedict et al., 2002) are two validated batteries which are most commonly used in assessments of patients with MS (Lovera & Kovner, 2012). More recently, Langdon et al. (2012) proposed a Brief International Cognitive Assessment for MS. Their proposed battery is aimed at providing an easy to administer, short-duration test, constructed specifically for maximum international use. However, despite the fact that these batteries were developed by consensus among professional groups within the field of MS, there still does not appear to be a general acceptance and application of these batteries. Ferreira (2010) posits that non-adoption of a single test battery may be due to the fact that there is still no agreement regarding the domains impacted by MS. Non-MS specific screening tests such as the Dem Tect Test and the Mini Mental Status Exam are often used by neurologists when assessing patients with MS. However these tests are

insufficient as they are not focused on cognitive domains typically impacted by the disorder (Engel, Greim, & Zettl, 2007), and may result in the underdiagnosis of cognitive decline in patients with MS. The assessments mentioned up to this point were developed using traditional paper-and-pencil type tests. There has however of recent been a marked increase in the number of assessments being adapted and developed using computerised applications.

2.4.5 Computerised test instruments

As indicated in the review of studies above, there has been a substantive body of research on cognitive performance in association with MS using paper-and-pencil tests. However, there has been a marked increase in the development of computerised neurocognitive assessments over the past decade and new tests and related research findings are being released on an ongoing basis for numerous clinical groups (Crook, Kay & Larrabee cited in Bauer et al., 2012). This is also true in the case of MS. Computerised neurocognitive assessments inherently have a number of advantages for the use with patients with MS. These include a short duration, reduction in practice effects and improved testing of reaction time and processing speed (Wilken et al., 2003). Rater burden and associated costs of traditional test batteries are also high. Computerised assessments often require a lower level of administrator training, whilst scoring is done automatically, resulting in reduced cost of testing. Information processing speed is considered to be one of the primary domains impacted by MS. Traditional measures cannot separate processing speed from other aspects of task performance (Edgar et al., 2011) and are not sensitive to subtle changes in information processing speed. In contrast, computerised assessments are able to measure reaction times in milliseconds (Wilken et al., 2003).

A number of computerised neurocognitive assessment tools have been developed and/or validated for the cognitive assessment of patients with MS. These assessment tools can be

divided into two main groups, depending on whether they test multiple or single cognitive domains. Single domain assessments include the Computerised Test of Information Processing, the Computerised Speed Cognitive Test and the Attention Network Test. Wojtowicz, Omisade and Fisk (2013) used the Computerised Test of Information Processing in an assessment of intra-individual variability of processing speed of patients with MS, indicating that this measurement provided "sensitive, unique and important information regarding cognitive functioning in early MS." A recent study (Ruet, Deloire, Charré-Morin, Hamel, & Brochet, 2013) evaluated the use of the Computerised Speed Cognitive Test in patients with MS. This study confirmed the test's validity and reliability to evaluate information processing speed and found that it had a high degree of sensitivity in the prediction of impairment. A study by Urbanek et al. (2010) confirmed the utility of the Attention Network Test computerised tool in assessing attention revealed specific impairments in the attentional functioning of patients with MS that could not be explained primarily by slowed processing speed.

Multiple domain tests that have been researched using patients with MS include the Cognitive Stability Index™ (Younes et al., 2007), the Automated Neuropsychology Assessment Metrics test (Wilken et al., 2003), the Mindstreams Computerised Cognitive Battery (Achiron et al., 2007), the Cognitive Drug Research System (Edgar et al., 2011) and the computerised version of the Minimal Assessment of Cognitive Function in Multiple Sclerosis battery (Lapshin, Audet, & Feinstein, 2014; Lapshin, Lanctôt, O'Connor, & Feinstein, 2013). Researchers recently adapted certain tests of the Minimal Assessment of Cognitive Function in Multiple Sclerosis battery for use as a computerised screening tool and found that it had significant sensitivity and specificity over across the entire disorder spectrum, from Clinically Isolated

Syndrome to Secondary Progressive MS (Lapshin, Audet, & Feinstein, 2014; Lapshin, Lanctôt, O'Connor, & Feinstein, 2013).

2.4.6 The Immediate Post Concussion Assessment and Cognitive Testing assessment tool

The Immediate Post Concussion Assessment and Cognitive Testing (ImPACT) computerised assessment tool was initially developed for the monitoring of recovery from mild concussive brain injuries. It is the most commonly used of all computerised neurocognitive screening tests within the sports arena worldwide, as well as in South Africa (Resch, McCrea, & Cullum, 2013; Shuttleworth-Edwards, Whitefield-Alexander, Radloff, Taylor, & Lovell, 2009). It is based on well-researched traditional neurocognitive tests and assesses domains of attention, memory and processing speed - domains typically affected by MS. Specifically the test yields a number of composite scores. These include composite scores of Verbal Memory, Visual Memory, Visual Motor Speed, Reaction Time and Cognitive Efficiency Index. Importantly, ImPACT is currently the only test of its kind to be registered with the Health Professions Council of South Africa (2010) as an approved test for clinical use in the country. In terms of the HPCSA regulation of South Africa (2010), the ImPACT test may be administered by a trained technician, whilst interpretation of results can only be done by a registered psychologist. It can be done in numerous languages including English and Afrikaans. It is mouse-driven and can be loaded on any standard computer and is also available on-line. Results from the various tests are combined to provide composite scores of functioning in the domains of verbal memory, visual memory, visual motor speed and reaction time. The reports are generated automatically and reflect percentile rankings for each composite score, ranked against age-adjusted USA norms. A South African study of predominantly white English-speaking scholars found that most scores

fell well within the normative bands of the age-related USA norms (Shuttleworth-Edwards et al., 2009).

A large body of research indicates that the ImPACT test has good psychometric properties. Resch et al. (2013) reviewed a number of computerised neurocognitive tests that are commonly used in cases of mild traumatic brain injury, including the ImPACT test. Regarding reliability of ImPACT, they found six published studies. These studies found reliability over the short-term (over a period of up to 50 days) ranging from a weak 0.23 (Verbal Memory) to a strong 0.88 for Processing Speed. Longer term studies (one to three years test-retest intervals) showed better reliability with a range of reliability coefficients from a moderate 0.46 (Verbal Memory) to a high 0.85 (Processing Speed).

An extensive study by Maerlender et al. (2010) confirmed the construct validity of all the ImPACT domains except for Impulse Control. This research followed an earlier study by Schatz and Putz (2006) which had indicated the construct validity of ImPACT's Reaction Time composite score. Maerlender et al. (2010) furthermore confirmed that the ImPACT subtests are heavily loaded towards working memory and processing speed (despite the fact that ImPACT has no specific working memory subtest). The multi-factorial nature of many of the ImPACT subtests was also reflected in the fact that many of the subtests correlated with multiple neurocognitive domains. This study also raised the question as to whether the Processing Speed and Reaction Time composites are indeed independent functions, as results indicated that these domains share considerable variance. They also found that the neurocognitive domain scores of motor function, attention and impulse control did not correlate with any of the ImPACT composite domain scores. Maerlender et al. (2013) further analysed the data of their 2010 study. Their results indicate that, whereas the test provides good construct sensitivity, there is a definite

lack in construct specificity. This is in line with earlier findings (Allen & Gfeller, 2011) which indicated that there did not appear to be a real differentiation between verbal and visual memory. The authors speculate that this may be due to the fact that the Word Memory tasks are presented in a visual manner (words on a screen). Research was also done to examine the concurrent validity of ImPACT (Allen & Gfeller, 2011). This study used tests traditionally included as part of "paper-and-pencil" assessments of concussion. They confirmed moderate to strong correlations between cognitive measures evaluating similar cognitive domains.

Besides its use for assessing mild traumatic brain injury, ImPACT has also been assessed for its applicability in cases of other types of neurological insults. The test has been shown to be sensitive to the effect of depression on cognitive performance, with Processing Speed and Reaction Time composites markedly compromised (Iverson, 2006). An initial small sample study indicated the sensitivity of ImPACT to cognitive late effects experienced by some brain tumour survivors (Conklin et al., 2013). The authors propose that ImPACT may be a useful test for the screening and monitoring of late effects, but that more comprehensive research needs to confirm this. ImPACT has also been evaluated for the use as a diagnostic tool for Minimal Hepatic Encephalopathy (Tsushima et al., 2013). Results indicate that ImPACT was more sensitive than previously reported traditional neurocognitive tests, whilst specificity was equivalent to traditional measures at an acceptable level of >90%. No reports could be found to date of any use of the ImPACT test in the assessment of patients with MS.

An expert committee of twelve members who took part in the development of the proposed Brief International Cognitive Assessment for MS screening test suggested that it should address the domains of information processing speed, verbal memory and visual memory (Langdon et al., 2012). Whereas the committee acknowledged that MS could present

impairments over a wide spectrum of cognitive domains, it was felt that in large clinical samples these three domains would identify a reasonable proportion of patients with cognitive impairment. These domains are specifically addressed by the ImPACT assessment and make this assessment tool a good candidate for possible use in the screening of patients with MS with the aim of monitoring progression of the disorder and possible rehabilitative interventions.

2.5 Aim and Rationale of the study

The literature review presented above highlights the fact that the early detection and ongoing monitoring of the impact of Multiple Sclerosis (MS) on cognition is of critical importance. Despite this, patients often do not receive a neurocognitive assessment, due to amongst others the lack of a neurocognitive assessment tool that is user friendly, and diagnostically appropriate for the purpose.

The ImPACT computerised assessment is one of the most widely used tools in the assessment of concussion in sport worldwide and has been shown to measure those domains of cognition that are most typically affected by MS including attention, visual memory, verbal memory and information processing speed. It is easy to administer and can be utilized for the ongoing monitoring of cognitive performance. It appears likely that the use of this tool with patients with MS would assist in the assessment and treatment of the cognitive related problems linked to the disorder. The primary aim of this study is therefore to determine whether ImPACT differentiates the cognitive performance of patients with MS from healthy controls for each of the cognitive domains measured by the tool.

As noted in the literature review, the use of the Symbol Digit Modality Test (SDMT) as a screening test for MS is well researched. This test has furthermore been shown to correlate with each of the composite scores of the ImPACT test using a sample of collegiate athletes with

concussion. A further aim of the current study is therefore to determine whether the correlation between SDMT scores and the ImPACT composite scores are also observable for samples using patients with MS and healthy individuals.

The utilisation of tests measuring incidental learning is not commonly employed when assessing cognitive performance in patients with neurological insults. However, following on from the literature review, it has been shown that the use of an incidental recall test, utilising an adapted SDMT test, might serve to distinguish between patients with MS and healthy controls. In addition, the review also indicated research where the added use of interference in incidental recall assessment using a vocabulary test had been found to be effective in a population of MS patients. An aim of the current study was to assess the utility of an adapted SDMT Delayed Recall test. The results from this test would furthermore be used for comparison with the outcome on the ImPACT Design Memory Delayed Recall subtest which also measures incidental recall with an interference component, in order to assess the utility of this subtest in the assessment of patients with MS.

2.6 Hypotheses

2.6.1 Hypothesis 1

The cognitive performance of patients with Multiple Sclerosis will be significantly worse than that of a group of Healthy Control individuals, as reflected in results of each of the composite scores of ImPACT assessment tool including Verbal Memory, Visual Memory, Visual Motor Speed, Reaction Time and the Cognitive Efficiency Index, as well as the SDMT test.

The rationale for this hypothesis is that the cognitive domains of information processing speed, verbal memory and visual memory are recognised as those most commonly affected by

MS (Langdon et al., 2012). These domains are specifically assessed by ImPACT and should therefore indicate worse performance in the patient group compared to the healthy control group. The SDMT test has been shown to be a reliable screening test to discriminate between patients with MS and healthy controls (see section 2.4.2 above).

2.6.2 Hypothesis 2

SDMT scores will be correlated with each of the composite scores of the ImPACT assessment tool including Verbal Memory, Visual Memory, Visual Motor Speed, Reaction Time and the Cognitive Efficiency Index, for the MS patient group and the control group, with the strongest correlations being recorded for the Visual Motor Speed and the Reaction Time composites.

The rationale for this hypothesis is as follows. Results from SDMT tests have previously been compared with those of the ImPACT test. A study using a sample of collegiate athletes with concussion found that SDMT correlates with each of the four ImPACT composite domain scores ($p < 0.01$), but more strongly with the Visual Motor Speed ($r = 0.70$) and Reaction Time ($r = -0.60$) composites of ImPACT than the two memory composites (Verbal Memory: $r = 0.46$; Visual Memory: $r = 0.37$) (Iverson et al., 2005). Furthermore, factor analysis from this same study found that SDMT and ImPACT's Visual Motor Speed composite and Reaction Time composite appear to be measuring a similar underlying construct. In an assessment of mild traumatic brain injury in children, results from the Paediatric ImPACT Response Speed Composite were also strongly correlated with SDMT scores (Newman, Reesman, Vaughan, & Gioia, 2013). To date SDMT scores have not been compared to ImPACT scores using populations of MS patients or healthy individuals.

2.6.3 Hypothesis 3

Performance results of MS patients will be significantly worse than the control group when comparing results of an SDMT Delayed Recall test.

The rationale for this hypothesis is as follows. Performance of incidental recall, as measured by an adapted SDMT recall test (Minden et al., 1990) and incidental recall with interference, using a verbal memory test (Coolidge et al., 1996) have separately indicated worse performance of patients with MS compared to healthy controls. The combination of both incidental recall and an interference component using an adapted SDMT test is hypothesized to accurately discriminate performance between the two test groups.

2.6.4 Hypothesis 4

Performance results of MS patients will be significantly worse than the control group when comparing results of the ImPACT Design Memory Delayed Recall subtest.

This hypothesis is formulated based on the same basic reasoning as for Hypothesis 3 namely that a delayed recall test would result in poorer performance by Patients with MS compared to Healthy Controls.

2.6.5 Hypothesis 5

Performance on the SDMT Delayed Recall test will be significantly correlated with the ImPACT Design Memory Delayed Recall subtest.

The rationale for this hypothesis is that the SDMT test (Spreen & Strauss cited in Iverson, Lovell, & Collins, 2005) and ImPACT's Design Memory test (M.R. Lovell, personal communication, March 29, 2016) are both believed to measure visual working memory and attentional processes. This hypothesis will test the assumption that the delayed recall of these tests should be correlated.

3. Method

A number of assessments were done to compare the cognitive performance of patients with Multiple Sclerosis with that of a cohort of healthy controls. Ethical approval for the research was obtained from the applicable universities' ethics committees. Written and signed informed consent was obtained from all participants. Participation in the study was voluntary and participants could withdraw at any stage of the procedure. Participants received no monetary compensation for taking part in the study.

3.1 Participants

Patients were initially recruited from the research group taking part in the Tygerberg Hospital study entitled "The development and commercialization of a comprehensive, gene-based, pathology supported intervention program for improved quality of life in patients diagnosed with Multiple Sclerosis". Additional patients were recruited via references from these participants. A healthy control group was recruited on the basis of convenience sampling from family, friends and referrals from patients. The initial selection of the participants was done in a manner such that healthy controls were matched demographically with the patient group in terms of age, race, gender, education level, and quality of education.

Patients identified for inclusion were those with a previous positive diagnosis of MS and who, in the preceding month, had not had a major MS relapse or been treated with corticosteroids. In addition, the following criteria were used for determining possible inclusion of MS patients or healthy controls in the study group: aged between 18 years and 60 years; minimum completion of Grade 10 in English or Afrikaans; a maximum failure of one grade at school; never previously identified as having a learning disability, the absence of other neurological or psychiatric disorders, or previous brain injury resulting in hospitalization; no

self-reported motor dysfunction of either hand. In addition, there were a number of exclusion criteria on the basis of which it was not necessary to exclude any of the identified participants: (i) Participants who were not willing to complete the tests or were not willing to sign the ethical forms; (ii) Individuals whose results on the finger tapping test indicated impairment of Hand Motor Dexterity (see section 3.2.1.1 for the impairment criteria of Worthington & De Souza, 1989); (iii) Individuals with an ImPACT Impulse Control composite score of greater than 30 implicating an invalid result (see Section 3.2.2.1 below).

On this basis a total of 29 MS patients and 20 healthy controls were assessed and included in the study. All participants indicated either English or Afrikaans as their home language. The two groups were similar in terms of home language composition. English was indicated as the home language in 38% (n=11) of the cases for the patient group, whilst the healthy control group had 40% (n=8) of such individuals. The gender composition of the two groups broadly confirms population epidemiological ratios with the patient group having 79% females (n=23) and the healthy control group 85% females (n=17). The patient group included four individuals (14%) who classified themselves as "coloured", compared to three in the healthy control group (15%) (The term "coloured" is the official terminology used to describe South African individuals of mixed race who make up approximately 9% of the population and who live predominantly in the Western Cape area of the country) (Statistics South Africa, 2012). All other participants classified themselves as white. The race composition of the groups is consistent with research mentioned earlier (see section 2.1.1) which indicates that whites are the race group predominantly affected by the disorder.

Quality of education during the apartheid era varied greatly across the South African race groups, and continues to be the case since democratization, and therefore information regarding

the constitution of the patient and healthy control groups was taken into consideration in terms of this educational parameter (Shuttleworth-Edwards, Gaylard & Radloff, 2013). Each group had two individuals who attended disadvantaged schools of the former Department of Education and Training Development schools initiated in the Apartheid era with all other participants having attended the well-resourced schools formerly reserved for white individuals in the apartheid era. Using t-tests the two groups were furthermore compared and found to be equivalent for age, years of education and performance on the two tests used to estimate premorbid intellectual ability (WAIS-III Vocabulary Scaled and WAIS-III Matrix Reasoning Scaled) ($p > 0.05$, in all instances) (see Table 1).

Table 1

Comparison of Patient and Healthy Control groups for Age, Years of Education, and WAIS-III Vocabulary and Matrix Reasoning subtest scores

	Patients with MS (n = 29) Mean (SD); (range)	Controls (n = 20) Mean (SD); (range)	*t*-value	*p*-value
Age	44.3 (8.8); (29, 58)	44.5 (7.3); (32, 56)	0.084	0.934
Years of Education	14.6 (2.6); (12, 21)	15.2 (3.2); (12, 23)	0.726	0.474
WAIS-III Vocabulary	12.2 (2.6); (4, 16)	12.7 (2.7); (6, 17)	0.655	0.518
WAIS-III Matrix Reasoning	12.6 (2.7); (5, 17)	13.7 (2.4); (9, 17)	1.434	0.150

3.2 Measures

There were two main areas of focus for the assessments conducted in this study, including (i) an evaluation of aspects which may have an impact on cognitive performance and warrant being controlled for the purpose of such a study (hand motor dexterity, cognitive reserve and depression), and (ii) tests of cognitive performance (ImPACT, SDMT and SDMT Delayed

Recall). The methodological indications derived from statistical analyses conducted on the control variables, are reported in the method section. The results of the neurocognitive assessments themselves are reported in the results section.

3.2.1 Control Variables

3.2.1.1 Hand Motor Dexterity

As the ImPACT assessment requires the use of a computer mouse it is important to confirm that the participant's motor function of the hand and specifically the index finger of the dominant hand is within the normal range of performance. The finger tapping test as described and evaluated by Worthington and De Souza (1989) was used to evaluate the speed of index finger movement. This test entails the standardized placement of the forearm and metacarpophalangeal joint of the index finger, following which the number of taps performed on the "=" sign of a Truly817-10 calculator during a period of 10s was determined. This test was done twice for both the dominant and the non-dominant hand. The average of the dominant hand's score was used for analysis. Individuals whose results on the finger tapping test of their dominant hand exceeded two or more standard deviations below the average would be considered impaired therefore warranting exclusion from the study (as per impairment criteria from Worthington and De Souza,1989). As indicated above, it was not necessary to exclude any individuals in terms of impairment of hand motor functioning on the dominant hand as per this criterion.

The relationship of Finger Tapping Test results to SDMT (age-adjusted values), the SDMT Delayed Recall and each of the composite ImPACT scores were investigated using correlation analysis. The correlational coefficients were small in all cases with none of them

reaching significance ($p \geq 0.05$, in all instances) (see Table 2). The implication is that hand motor dexterity was unlikely to have been a significant contributing factor to performance on any of the neurocognitive tasks. Consequently it was considered that there was no indication for the results of the Finger Tapping Test to be used as a covariate in the neurocognitive comparative analyses.

Table 2. Correlational Analyses of the Finger Tapping Test of the dominant hand with the Symbol Digit Modalities Test and ImPACT Composite scores

	Patients with MS (n = 29) r (*p*-value)	Controls (n = 20) r (*p*-value)
ImPACT		
Verbal Memory	-0.146 (0.449)	-0.238 (0.334)
Visual Memory	0.005 (0.979)	-0.005 (0.983)
Visual Motor Speed	-0.027 (0.888)	-0.017 (0.943)
Reaction Time	0.140 (0.470)	-0.221 (0.349)
Cognitive Efficiency Index	-0.130 (0.502)	0.061 (0.790)
SDMT		
Age-adjusted Score	-0.229 (0.232)	0.145 (0.541)
Delayed Recall	-0.284 (0.135)	0.006 (0.981)

3.2.1.2 Cognitive Reserve

Cognitive Reserve is thought to protect patients with MS against cognitive decline (see section 2.2.3.4 above). An indication of Cognitive Reserve is often gained by estimating premorbid intelligence (see Benedict et al., 2010). A number of methods for establishing an estimate of premorbid IQ have been developed which utilise a combination of demographic data and results from subtests of the Wechsler Adult Intelligence Scale Revised (WAIS-R) and the

Wechsler Adult Intelligence Scale Third Edition (WAIS-III) (Wechsler, 1997), using those subtests which are deemed to have the best "hold" (i.e. resistant to deterioration) characteristics (Axelrod, Vanderploeg, & Schinka, 1999; Schoenberg, Scott, Duff, & Adams, 2002). Two such subtests commonly use are the Vocabulary and Matrix Reasoning subtests (Schoenberg et al., 2002). Premorbid intelligence was estimated using the Vocabulary and Matrix Reasoning subtests of the WAIS-III. The WAIS-III is currently the only version of the more recent editions of the WAIS i.e., WAIS-III and WAIS-IV (Wechsler, 1997; Wechsler, 2008, respectively) that has been translated into Afrikaans. This translation of the verbal subtests is provided as part of the South African WAIS-III standardisation manual (Claassen, Krynauw, Holtzhausen, & Mathe, 2001). It must be noted that, although it has not been standardised, a study of this translation has provided "... support for the reliability of the translated subtests as well as some support that the Afrikaans version is measuring intelligence in a manner similar to the English version" (Grieve & van Eeden, 2010, p. 267).

Interpretation of results from tests such as the WAIS-III should be done with consideration to possible factors that may influence results. A number of studies have shown that variables such as degree of acculturation, socio-economic status and level of education impact on cognitive test performance (Andrews et al., 2012; Fike et al., 2012). South Africa has a legacy of apartheid-inspired race-based differences in the quality of education that was provided. Research has found that these differences have a significant impact on results from the WAIS-III tests, both on verbal tasks that call upon acquired knowledge as well as on non-verbal performance tasks that are affected by test-taking sophistication (Shuttleworth-Edwards, Gaylard & Radloff, 2013). From the above it is clear that a study of this nature should control both for estimates of premorbid ability as well as for possible confounding factors such as level and

estimated quality of education. Level and quality of education was controlled for by ensuring that the composition of the sample groups matched on these particular factors (see section 3.1 above). These tests were done in the participants' language of choice of either English or Afrikaans and were administered and scored in accordance with the guidelines as per the WAIS-III UK Administration and Scoring manual (Wechsler, 1997).

As indicated above (Table 1) there were no differences in an estimate of premorbid ability as tested on the Vocabulary and Matrix Reasoning subtests of the WAIS-III.

3.2.1.3 Depression

Various tools have been developed for the assessment of depression levels. One of the most commonly used and most widely researched depression assessment tools is the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). This is a 21 question self-report inventory of depression with scores ranging between 0 and a maximum of 63. The following broad levels of depression classes have been identified: Minimal (0-13), Mild (14-19), Moderate (20-28) and Severe (29-63) (Beck, Steer & Brown, 1996). This inventory was originally developed for research purposes. It has subsequently been adapted to meet the requirements of the DSM-IV (BDI-II; The Psychological Corporation). Although it has never been specifically validated for MS, it is commonly used in clinical and therapeutic trials of patients with MS (Zephir et al., 2003). When interpreting the BDI scores it is important to consider that the presence of a disorder such as MS can inflate the results of specific questions designed to measure the somatic aspects of depression (Clark, Cavanaugh, & Gibbons cited in Aikens et al., 1999). Aikens et al. (1999) evaluated proposals by Mohr et al. to omit certain questions with a somatic loading, but came to the conclusion that there appeared to be no

measurable advantage in reducing the 21 item questionnaire for use with patients with MS. Participants completed the BDI-II inventory as an indicator of their level of depression.

The relationship of BDI-II results and the various tests of cognition was evaluated with correlational analysis. For MS patients there was one isolated significant correlation in that the BDI-II was negatively correlated with the Visual Motor Speed composite score ($p = 0.031$, see Table 3). There were no other significant correlations with any of the neurocognitive tests for either the MS patient or healthy control groups ($p \geq 0.050$, in all instances). While the mean BDI-II score for the MS patient group was somewhat higher than the mean BDI-II score for the control group (12.45 ± 9.61 and 5.75 ± 5.75, respectively), both mean scores fell within the BDI-II ''Minimal'' range of depression which has a cut-off level of 13 (see Beck, Steer & Brown, 1996), rather than the mild (14-19), moderate (20-28) or severe (29+) ranges of depression. Taking the standard deviations into consideration, a small number of MS patients may at worst have achieved scores bordering on the mild to moderate range. It is not expected that depression will impact negatively on cognition unless the level is severe (Bieliauskas, 1993). Therefore, given the relatively low levels of depression in the sample, that were broadly equivalent at an overall minimal level, taken together with the overriding absence of any significant correlation between BDI-II scores and the neurocognitive results, it was decided that covariate analysis of the neurocognitive results to control for the depression variable was not indicated for the purposes of this research.

Table 3

Correlational Analyses of the Becks Depression Inventory with ImPACT, the Symbol Digit Modalities Test (SDMT) and SDMT Delayed Recall test

	Patients with MS (n = 29) r (*p*-value)	Controls (n = 20) r (*p*-value)
ImPACT		
Verbal Memory	-0.361 (0.054)	0.435 (0.055)
Visual Memory	-0.351 (0.062)	-0.129 (0.587)
Visual Motor Speed	-0.401 (0.031)	-0.252 (0.284)
Reaction Time	0.179 (0.353)	0.097 (0.683)
Cognitive Efficiency Index	-0.171 (0.376)	0.192 (0.418)
SDMT		
Age-adjusted Score	-0.368 (0.050)	-0.054 (0.821)
Delayed Recall	-0.163 (0.397)	-0.168 (0.479)

3.2.2 Cognitive Tests

3.2.2.1 ImPACT

The Immediate Post Concussion Assessment and Cognitive Testing (ImPACT) computerised assessment tool was initially developed for the monitoring of recovery from mild concussive brain injuries. Currently it is considered to be the tool most widely used specifically in sports related injuries (Resch, McCrea, & Cullum, 2013; Shuttleworth-Edwards, Whitefield-Alexander, Radloff, Taylor, & Lovell, 2009). The tool measures performance on a number of cognitive domains deemed to be of primary importance when assessing cognition in patients with MS (Langdon et al., 2012) viz. processing speed, verbal memory and visual memory. In South Africa there is the immediate advantage, as indicated above (see section 2.4.6), that the ImPACT test is the only assessment tool of its kind that is currently registered for clinical use.

More generally the idea of using the ImPACT test is motivated by the fact that neurologists, neurosurgeons, medical doctors in general practice, and psychologists involved with neurocognitive assessments who are already using the ImPACT test in the context of concussive brain injury, would probably favour being able to employ an assessment tool with which they are already familiar. Finally, while primarily a neurocognitive test, the ImPACT test also has a symptom check list incorporated into the programme. Information elicited by this checklist can be incorporated into the automated report. The check list applies to symptoms commonly resulting from concussion, but would apply to neuropathological symptoms emanating from brain dysfunction more generally. Therefore, while the present research is restricted to the cognitive profiles of MS only, it is likely that the adjunct of the ImPACT symptom questionnaire would be considered an added advantage for clinicians using the test in the context of evaluating MS sequelae with their patients.

Version 2.0 of ImPACT test was downloaded via the internet for offline application onto a laptop computer. The ImPACT test consists of six tests. These tests are as follows:

(1) Word Discrimination: participants are presented with 12 target words for a duration of 750ms each (twice to facilitate learning of the list). Recall is then tested by presenting 24 words, which include the 12 target words. Following the presentation of all the other test modules, delayed recall is tested by again presenting the 24 words in a similar manner. This test evaluates attentional processes and verbal recognition memory.

(2) Design Memory: participants are presented with 12 target designs for a duration of 750ms each (twice to facilitate learning of the list). Recall is then tested by presenting 24 designs, which include the 12 target designs. Following the presentation of all the other test modules, delayed recall is tested by again presenting the 24 designs in a similar

manner. This recall is tested without alerting the participant at initial presentation that later recall will be tested. This test evaluates attentional processes and visual recognition memory as well as incidental learning

(3) X's and O's: a computer generated screen with randomized X's and O's are presented for a period of 1,5s. Three of the X's or O's are presented in yellow. A timed distracter task then follows during which the participant is required to press the "Q" key if a blue square is displayed and the "P" key if a red circle is displayed. On completion of the distracter task the subject is requested to recall the location of the highlighted X's and O's. This test evaluates visual working memory and visual processing speed.

(4) Symbol Matching: nine common symbols (e.g. circle, square, arrow), each with its associated number (1-9) directly below it, are displayed on the screen. The participant must then, as quickly as possible, click on the corresponding number associated with each of the symbols presented. This test evaluates visual processing speed, learning and memory.

(5) Colour Match: a word (RED, GREEN or BLUE) is presented in a box on the screen. The participant must click on the box as quickly as possible in each case where the colour of the ink in which the word is displayed matches the word. This test evaluates reaction time, impulse control, and response inhibition.

(6) Three-letter Memory: three consonant letters are displayed on the screen, followed by a distracter task. 25 buttons (ranging from 1 – 25) are presented in a randomized 5 x 5 grid. In this timed test participants must sequentially click as many buttons as possible in a backward order starting from 25. Following this, participants are asked to recall the

three letters initially displayed. This test evaluates working memory and visual-motor response speed.

Each of the above six tests may contribute to one of six ImPACT composite scores:

(1) Verbal Memory composite: this score is calculated by adding the averages scores for the Word Discrimination, Symbol Matching and Three-letter Memory tasks. It is thought to evaluate attentional processes, learning and memory.

(2) Visual Memory composite: this is calculated by taking the average of the total percent correct of the Design Memory and the X's and O's modules. Aspects of attention and scanning, learning, and memory are evaluated.

(3) Visual Motor Speed composite: the average of the following two results are calculated: the average of the total number correct during interference of X's and O's (module 3), and the average Counted Correctly during the Countdown phase in the Three Letter Memory task (module 6). Processing, learning and memory, and visual-motor response speed is assessed by this composite.

(4) Reaction Time composite: the average of the following scores are calculated: the average correct reaction time of the interference stage of X's and O's, the Symbol Match average correct response time, and the Colour Match average correct time. This score evaluates average response speed.

(5) Cognitive Efficiency Index: this index was developed to provide an indication of the trade-offs between speed and accuracy. Utilizing the Symbol Match module, speed is measured by the number of items correctly clicked, while accuracy is the number of items correctly identified at the end of the test (the memory component). The following formula is used to calculate this measure:

CEI = (1-(symbolMatchAverageCorrectRTvisible/3)) *

(symbolMatchTotalCorrectHidden/9)

(6) Impulse Control composite: this score is obtained by adding the total incorrect on the interference phase of the X's and O's modules to the total of the Colour Match commissions. It is a measure of the validity of the test and identifies participants who were either confused about test instructions or did not put in maximum effort in completion of the test. Test results with a value greater than 30 should be discarded (Lovell, 2012).

ImPACT does have age-adjusted percentiles for each of the other five composite scores. However, these norms were developed based on a population of active athletes (Lovell, 2011). Furthermore, the analysis of the demographics of participants in this study indicated that the patient and healthy control groups were highly equivalent for age range and mean age (Patients age range: 29 – 58; Healthy Controls age range: 32 – 56; Patients mean age = 44.31 ± 8.78; Healthy Controls mean age = 44.50 ± 7.29; $p = 0.935$; Patients n = 29, Healthy Controls n = 20) (see section 3.1). The unadjusted composite scores achieved by each participant were therefore used for analyses. In addition, scores achieved on the incidental learning of Design Memory were also utilised for comparison to a similar test.

3.2.2.2 SDMT

The Symbol Digit Modalities Test (SDMT; Smith, 1982) is one of the most commonly used single screening tests for cognitive impairment, and has been shown to be effective in the assessment of patients with MS (Parmenter et al., 2007; Sonder et al., 2014). It is an easy to administer paper-and-pencil test which is user-friendly and only takes a few minutes to complete with minimal use of equipment. The test consists of a stimulus page containing nine symbols,

each paired with a single digit. The remainder of the page consists of a pseudo-randomized sequence of the symbols. Participants are required to match the symbols with its paired digit, attempting to correctly match as many as possible symbols within a timed period of 90s. As per the recommendations of the Minimal Assessment of Cognitive Function in Multiple Sclerosis panel (Benedict et al., 2002), the SDMT test was administered orally in order to minimize the possible impact of upper-extremity weakness or loss of coordination. The score is the number of correct symbols paired with the appropriate numbers. Centofani (1975) produced age-based norms for a non-clinical population sample. Using these norms each participant's SDMT score was transformed to a normalized age-adjusted value by using the following statistical transformation:

(SDMT score – Normed SDMT Average value for age)/Normed SDMT Standard Deviation for age).

3.2.2.3 SDMT with Incidental Learning

Incidental learning is not often used in the assessment of brain disorders (Demakis et al., 2001; Lezak et al., 2012). Utilisation of an adapted SDMT Incidental Learning task indicated that patients with MS performed significantly worse than healthy controls (Minden et al., 1990). Furthermore, research utilising an interference task together with verbal memory tests also resulted in patients with MS performing significantly worse than a healthy control group (Coolidge et al., 1996). The adapted SDMT Delayed Recall task was therefore applied in the current research in order to assess its ability to distinguish between patients with MS and a healthy control group. Following the standard administration of the SDMT test, the WAIS-III Vocabulary subtest was administered serving as an interference task. Following this the participants were provided with the nine symbols used in the Symbol Digit Modalities Test. They were then requested to attempt to recall as many of the paired digits for each of the

symbols as possible. There was no prior warning that this would be a subsequent requirement. The number of correctly recalled symbols was used as the final score.

3.3 Assessment Procedure

Participants were interviewed to obtain demographic data as well as information related to factors that needed to be controlled for using a structured interview approach (see Appendix A). These interviews were conducted by the researcher, a psychology Masters student. In order to minimize the possible impact of aspects such as fatigue and heat, assessments were normally done during the early morning. In rare cases where patients indicated problems with an early morning assessment an alternative time was agreed upon. This was done on the condition that fatigue and heat would not be a factor for such patients. The selection of the location of the assessment was furthermore done to ensure that heat was not a problem and that no external disturbances would cause distraction.

All assessments were conducted by the researcher who was trained in the administration of the various tests. This training, as well as the administration of all the assessments, was done under the supervision of a registered clinical psychologist with experience in the administration of the WAIS-III and the additional paper-and-pencil tests, and who is credentialed in the administration of the ImPACT test.

A standardized procedure was utilized during the assessment of participants. The procedure was as follows:

a) Welcome participant and explain procedure.

b) Explain consent form and complete should participant accept conditions.

c) Explain and conduct each assessment in the following order:

- Patient demographic data interview (see Appendix A)

- Finger Tapping Test
- ImPACT test
- WAIS-III Matrix Reasoning test
- SDMT test
- WAIS-III Vocabulary test
- SDMT Delayed Recall test
- BDI-II self-report

3.4 Data analyses

All data were analysed using the IBM SPSS Statistics v22 statistical analysis computer package. Preliminary analyses were done to determine whether the MS patient group and the healthy control group were similar for various identified factors which may have an influence on their cognitive performance. Specifically the two groups were compared for demographic data (age, years of education completed) performance on the WAIS-III Vocabulary and Matrix Reasoning subtests. Further, correlational analyses were conducted to identify whether Hand Motor Function (as tested by a finger tapping test) and depression (as per the BDI-II self-report) might require inclusion as covariates in the principal analyses. Finally, analyses in terms of the neurocognitive variables were done. Independent t-test analysis was used to compare performance of the MS patients and controls on the ImPACT, ImPACT Design Memory Delayed Recall subtest, SDMT and the SDMT Delayed Recall test. In addition, correlational analysis was used to explore the correlation between the ImPACT composite scores and SDMT, and the correlation between the ImPACT Design Memory Delayed Recall subtest and the SDMT Delayed Recall test.

Bonferroni adjustments may be indicated when interpreting the results of a study employing multiple measures with a view to protecting against Type I error (finding significance that is erroneous). For the purposes of this study, however, a decision was taken not to apply the Bonferroni's adjustment in the interests of protecting against Type-II error (i.e. failing to find true significance where it exists) (Brandt, 2007), with the following rationale.

In terms of the typical neuropsychological test battery used in a comprehensive clinical or research situation, the current study is considered to have employed a relatively small and focused battery, incorporating only two tests (ImPACT and SDMT). In turn these tests, including their subtests, broadly incorporate only two functions, processing speed and memory. For the purposes of Bonferroni's adjustment this might warrant dividing the p-value of 0.05 by two, and creating an adjusted significance value of $p = 0.025$. On this basis, all the relevant ImPACT results that were significant would remain significant. However, the SDMT would fail to reach significance (see results section to follow), despite the contradictory evidence of a medium effect size of clinical relevance, and as such can be considered to be a Type II error. Such a non-significant finding for the SDMT is contrary, also, to what would be expected from the research literature that supports the sensitivity of the SDMT as a discriminatory screening tool for MS patients, in turn clearly supporting a decision against the introduction of a Bonferroni's adjustment for this study.

Further reasons not to increase the stringency of the significance value for this study via the use of Bonferroni's adjustment are the relatively small sample size, and the heterogeneity of an MS sample. These are both factors that would predispose the study to Type II error in the evaluation of group brain injury outcome (Brandt, 2007), i.e., failure to detect significant differences of prime clinical relevance where they exist. The misapplication of Bonferroni's

adjustment in a brain impairment study that leads to overlooking critical clinical insights is strongly criticized by leading researchers in the discipline, with Brandt (2007) going so far as listing such erroneous use of the procedure as a neuropsychological “crime” or “misdemeanour”.

4. Results

The results of the analyses of the various tests performed are presented below in the following sequence:

a) T-test comparative analyses of MS Patients and Controls performance on the ImPACT composite scores.

b) T-test comparative analysis of MS Patients and Controls performance on the SDMT

c) Correlational analyses of the ImPACT composite scores with the SDMT

d) T-test comparative analyses of MS Patients and Controls performance on the ImPACT Design Memory Delayed Recall subtest and the SDMT Delayed Recall test.

e) Correlational analysis of the ImPACT Design Memory Delayed Recall subtest and the SDMT Delayed Recall test.

4.1 T-test comparative analyses of MS Patients and Controls on ImPACT

There was an overall consistent trend for patients to perform worse than controls on each of the ImPACT composite scores. Two of the ImPACT composite scores viz. Reaction Time and Cognitive Efficiency Index ($p < 0.05$ in both instances) produced differences that were statistically significant and were accompanied by medium to high effect sizes of clinical relevance in that the confidence intervals did not contain 0 (-0.735, CI = −1.320, −0.142 and 0.690, CI = 0.102, 1.273 respectively). A further two composite scores, Visual Motor Speed and Verbal Memory had differences that approached significance ($p = 0.061$, and $p = 0.065$, respectively) (see Table 4 below).

4.2 T-test comparative analyses of MS Patients and Controls on the SDMT

Patients performed significantly worse than the Healthy Controls for the SDMT ($p < 0.05$) (see Table 4 below). The result for this score was accompanied by a medium effect size of clinical relevance in that the confidence interval did not contain 0 (0.592, CI = [0.050, 0.977].

It is of note that whereas results on both ImPACT and SDMT indicate poorer performance by the patient group as a whole, the wide range of performances points to the fact that certain individuals diagnosed with MS performed at a very high level. The wide variation in performance is further consistently endorsed by the much higher standard deviations for the MS group compared with the healthy controls with respect to all the neurocognitive test scores.

Table 4

T-Test comparisons of MS patients and controls on ImPACT and the Symbol Digit Modalities Test (SDMT)

	Patients with MS (n = 29) Mean (SD) Range	Controls (n = 20) Mean (SD) Range	*t*-value	*p*-value	Effect size, δ 95% CI
ImPACT					
Verbal Memory	80.14 (15.85) 32, 100	87.40 (7.80) 66, 100	1.892	0.065	0.550 -0.032, 1.128
Visual Memory	64.14 (14.96) 35, 90	69.45 (13.53) 45, 96	1.269	0.211	0.370 -0.206, 0.942
Visual Motor Speed	29.98 (7.45) 17.55, 46.00	33.70 (5.29) 23.45, 44.43	1.921	0.061	0.558 -0.026, 1.137
Reaction Time	0.79 (0.16) 1.16, 0.59	0.69 (0.09) 0.86, 0.52	-2.528	0.015*	-0.735 -1.320, -0.142
CEI**	0.11 (0.24) -0.87, 0.38	0.25 (0.13) -0.06, 0.48	2.375	0.022*	0.690 0.102, 1.273
SDMT					
Age-adjusted Score	-0.63 (1.28) -3.27, 1.26	-0.03 (0.81) -1.26, 2.20	2.038	0.047*	0.592 0.050, 0.977

*$p < 0.05$
** CEI = Cognitive Efficiency Index

4.3 Correlational analyses of ImPACT with the SDMT

The relationships between the SDMT results and each of the ImPACT tests were investigated using correlational analysis. Significant correlations were found for each of the composite scores for the Patient Group with the SDMT scores ($p < 0.05$, in all instances) except for the Verbal Memory composite score ($p = 0.124$). The Healthy Control group had significant correlations for the Visual Motor Speed, Reaction Time and Cognitive Efficiency Index composites scores, while correlations for the Verbal Memory ($p = 0.770$) and Visual Memory ($p = 0.081$) composite scores were not statistically significant (see Table 5).

Table 5

Correlational analyses of the ImPACT test scores with the Symbol Digit Modalities Test

	Patients with MS (n = 29) r (*p*-value)	Controls (n = 20) r (*p*-value)
ImPACT		
Verbal Memory	0.292 (0.124)	0.070 (0.770)
Visual Memory	0.426 (0.021)*	0.399 (0.081)
Visual Motor Speed	0.775 (<0.001)*	0.611 (0.004)*
Reaction Time	-0.713 (<0.001)*	-0.553 (0.011)*
Cognitive Efficiency Index	0.414 (0.026)*	0.478 (0.033)*

*$p < 0.05$

4.4 T-test comparative analyses of MS patients and controls on the ImPACT Design Memory Delayed Recall subtest and the SDMT Delayed Recall test

Results of both the ImPACT Design Memory Delayed Recall subtest as well as the SDMT Delayed Recall test were compared between the MS patient and control groups using the t-test. MS patients scored significantly worse than controls on the ImPACT Design Memory Delayed Recall subtest (Patients: n=29; M ± SD = 66.45 ± 14.58; Controls: n = 20; M ± SD = 79.20 ± 13.52; $p < 0.05$). The result for this score was accompanied by a large effect size of clinical relevance in that the confidence interval did not contain 0 (0.902, CI = [0.229, 1.494]) (see Table 6).

Patients also scored significantly worse than controls for the SDMT Delayed Recall test (Patients: n=29; M ± SD = 3.31 ± 2.44; Controls: n = 20; M ± SD = 5.10 ± 2.86; $p < 0.05$). The

result for this score was accompanied by a medium effect size of clinical relevance in that the confidence interval did not contain 0 (0.684, CI = [0.062, 0.990]) (see Table 6).

Table 6

T-Test comparisons of MS patients and controls on the ImPACT Design Memory Delayed Recall subtest and the Symbol Digit Modalities Test (SDMT) Delayed Recall test

	Patients with MS (n = 29) Mean (SD) Range	Controls (n = 20) Mean (SD) Range	*t*-value	*p*-value	Effect size, δ 95% CI
ImPACT					
Design Memory Delayed Recall	66.45 (14.58) 50, 100	79.20 (13.52) 54, 100	3.098	0.003*	0.902 0.229, 1.494
SDMT					
Delayed Recall	3.31 (2.44) 0, 9	5.10 (2.86) 0, 9	2.352	0.023*	0.684 0.062, 0.990

*$p < 0.05$

4.5 Correlational analysis of the ImPACT Design Memory Delayed Recall subtest with the SDMT Delayed Recall test

The analysis indicates a significant relationship between the two tests for each of the individual groups assessed. Results were as follows: Patients: n = 29, r = 0.491; Controls: n = 20, r = 0.447 ($p < 0.05$ in all instances).

5. Discussion

The primary aim of this study was to determine whether the Immediate Post Concussion Assessment and Cognitive Testing (ImPACT) computerised assessment tool could differentiate between the cognitive performance of patients with Multiple Sclerosis (MS) and that of a healthy control group. This would indicate the possible utility of ImPACT as a screening and monitoring tool in this population group. A secondary aim of this study was to determine the correlation between the SDMT test and each of the ImPACT composite scores for patients with MS and for healthy individuals. Previous studies have indicated correlations between these two tests using a collegiate athlete sample group (Iverson et al., 2005). A number of studies have confirmed SDMT as an effective screening tool for cognitive impairment in MS patients (see section 2.4.2). Correlations between the SDMT and ImPACT would support the findings of Iverson et al. (2005) and also strengthen the validity of ImPACT as a screening tool for cognition in MS patients.

A final aim of this study was to investigate the utility of delayed incidental learning tasks (i.e. incidental recall following interference). Prior research has produced conflicting results in the ability of *immediate* incidental recall tests to discriminate between MS patients and controls (see section 2.4.3). A previous study has indicated that a verbal *delayed* incidental recall task (which includes interference during administration) had discriminatory value when comparing performance by MS patients with healthy controls (Coolidge et al., 1996). To the author's knowledge the current study is the first to assess *visual delayed* incidental recall performance for this population group. The SDMT Delayed Recall test, and the ImPACT Design Memory Delayed Recall subtest were employed for this purpose. Confirmation of the utility of the ImPACT Design Memory Delayed Recall subtest as a screening tool would further enhance the

value of ImPACT in its application for cognitive screening of this population. The value of the incidental recall tasks in the MS patient population group – which typically has elevated levels of depression – is that incidental learning does not appear to be affected by depression (see section 2.4.3).

This discussion of results is guided by a set of hypotheses informed by the literature review (see section 2). A cross-sectional study was done comparing the cognitive performance of a group of MS patients (n=29) with that of a healthy control group (n=20), using ImPACT, SDMT and the SDMT Delayed Recall test. The groups were controlled for in order to ensure equivalence in terms of age, level of education, and standard of education, factors that have been shown to impact on the cognitive performance of individuals. Cognitive reserve, as indexed by premorbid intelligence, is known to be a protective factor against cognitive decline in patients with MS (see section 2.2.3.4). Premorbid intelligence was estimated using two subtests of the WAIS-III intelligence test which have been shown to be resistant to neurological insult viz. Vocabulary and Matrix Reasoning. Analysis indicated that the sample groups were equivalent on both of these subtests. The ImPACT test requires use of the subject's index finger. Hand motor dexterity of the dominant hand, was consequently assessed. Correlational analysis indicated no significant correlations between the dominant hand's index finger motor dexterity and the ImPACT, SDMT or SDMT Delayed Recall test. Consequently, hand motor dexterity was not taken into consideration in the analysis of performance on neurocognitive tests. Participants were also requested to complete a self-assessment of their level of depression that revealed levels of depression predominantly in the "Minimal" range (see section 3.2.1.3) for both groups. In a series of correlational analyses, there was only one isolated significant correlation of depression with a neurocognitive test viz. the ImPACT Visual Motor Speed composite score.

Consequently, taken overall, it was decided that the levels of depression were not sufficient to have substantively affected the results on the neurocognitive tests. Based on the above, it is considered that the comparative group outcomes of the various neurocognitive evaluations are unlikely to have been impacted in any significant way by the above-mentioned control factors, including age, level and quality of education, premorbid level of intellectual function, hand motor dexterity and depression. Against this background a discussion of the results follows.

5.1 Performance of MS patients compared to controls as assessed by ImPACT

It was hypothesised that patients with MS would perform significantly worse than healthy controls on each of the ImPACT composite scores. Overall the results of the study lent support to this first hypothesis, in that there was a consistent trend for the MS patient group to perform worse than the controls on each of the ImPACT composite scores. In two instances the differences in performance were found to be significant with high to medium effect sizes of clinical relevance viz., Reaction Time and Cognitive Efficiency Index. Notably, the differences as measured by the Visual Motor Speed and the Verbal Memory composite scores did not reach significance although they approached significance.

Processing speed is one of the aspects of cognition most commonly and most significantly affected by MS (see section 2.2.2.1 above). Both the Reaction Time and the Cognitive Efficiency Index composite scores have a strong processing speed component. Previous research has suggested that the Visual Motor Speed and Reaction Composite are very similar and may not be independent functions (Maerlender et al., 2010). The fact that the Visual Motor Speed only approached significance in discriminating between the MS Patient and control group may possibly be explained when considering that, besides the processing speed

component, this composite score also comprises an aspect of visual memory. Visual Memory was found to be the least able to discriminate performance between the two groups. This may have contributed to the Visual Motor Speed composite having lower discriminatory value. From the above it is clear that the other two ImPACT scores with a processing speed component, i.e., Reaction Time and Cognitive Efficiency, and possibly less of a strong visual component, are well-suited to discriminate between a MS patient group and healthy controls.

Each of the composite scores (including those where the difference in performance was not statistically significant), when taking the ranges and standard deviations into account, descriptively indicated greater variability in the performance by the MS patient group compared to that of the control group. This finding indicates that the MS patient group is likely to include participants who are relatively cognitively impacted as well as some who are cognitively spared. This heterogonous presentation of cognitive performance of the patient group is typical of Multiple Sclerosis which varies widely in terms of the areas of cognition and degree of impact which is affected in patients (see section 2.1.1).

5.2 Performance of MS patients compared to controls as assessed by SDMT

It was hypothesised that MS patients would perform significantly worse than healthy controls on the SDMT. This was indeed the case, supporting this hypothesis. A number of previous studies have confirmed the utility of the SDMT as a screening test for cognitive performance in MS patients (see section 2.4.2) and this study further confirms these findings.

5.3 Correlation between ImPACT composite scores and SDMT

It was hypothesised that SDMT scores would be correlated with each of the ImPACT composite scores for both the MS patient group as well as the healthy control group, with the

strongest correlations being with the Visual Motor Speed and Reaction Time composites. For both groups significant correlations were found for the Visual Motor Speed, Reaction Time and Cognitive Efficiency Index composite scores, of which the first two were also the strongest correlations. Correlations with both the Verbal Memory and Visual Memory composite scores were weak or not significant. Results of this study therefore partially satisfy this hypothesis, supporting existing literature which indicates that the Visual Motor Speed and Reaction Time composites appear to measure similar underlying constructs as the SDMT (Iverson et al., 2005). These results, coupled with the confirmation on prior research of the SDMT as an effective screening tool for MS patients, adds further support to the utility of ImPACT as a screening tool for this population group.

5.4 Performance of MS patients compared to controls using delayed recall tests

It was hypothesised that MS patients would perform significantly worse than the healthy controls on both the ImPACT Design Memory Delayed Recall subtest and the SDMT Delayed Recall test. This was indeed the case, pointing to the fact that interference on incidental learning tasks appears to create difficulties for the patient group. Furthermore, results indicated that the ImPACT Design Memory Delayed Recall subtest had a markedly higher effect size than the SDMT Delayed Recall test, and may therefore be more able to identify cognitive impairment in MS patients. Importantly, as discussed earlier, the ImPACT Visual and Verbal Memory composites did not distinguish between the MS patient and control groups, although there was a strong trend in that direction. These composites are made up of a combination of immediate and delayed recall components. Therefore it is noteworthy that in contrast to the findings for the ImPACT Visual and Verbal Memory Composite scores, the ImPACT Design Memory Delayed

Recall subtest was strongly discriminatory of the MS patient group relative to the controls, revealing a high, clinically relevant effect size. This links with the literature that suggests that visual recall is a good discriminatory function in MS patients (Chiaravalloti & DeLuca, 2008), taken together with the fact that the literature indicates that delayed recall (verbal) is also a discriminator of this population from controls (Coolidge et al., 1996).

Finally, it is of prime relevance that whereas immediate recall may be affected by depression due to poor motivation or impaired concentration, delayed incidental learning is thought not to be affected by depression, in that once something is learned it is likely to be retained (Šoštarič & Zalar, 2011). In contrast, such retained learning in the delayed condition is typically not the case in the brain impaired individual, whose ability to recall material is strongly challenged by the interference factor associated with the delayed recall task. Given that elevated levels of depression is a common feature in MS patients the above results add further value to the use of the ImPACT test as a screening tool to detect the presence of organically induced cognitive dysfunction in MS patients, particularly in the memory area. Furthermore, the greater fall-off for delayed recall in this study (ImPACT Design Memory Delayed Recall subtest) compared with the recall task incorporating both immediate and delayed recall functions (Visual Memory composite), provides a measure of support for the methodological rationale in this study that depression in the participants was not having a significant influence on the cognitive outcome. Were depression alone the core influential factor, this highly significant dissociation of a strong fall-off in delayed recall relative to a non-significant fall-off for a composite of immediate and delayed recall, is unlikely to have occurred.

5.5 Correlation of the ImPACT Design Memory Delayed Recall subtest with the SDMT Delayed Recall test

It was hypothesised that results from these two tests would be correlated. Whereas the SDMT and ImPACT's Design Memory test with Immediate Recall appear to measure the same constructs (Spreen & Strauss cited in Iverson, Lovell, & Collins, 2005; M.R. Lovell, personal communication, March 29, 2016) it was unclear whether the delayed recall of these tests would be correlated. These results satisfy the hypothesis that they are indeed correlated and that the delayed recall applications may also measure the same constructs. Cumulatively the various correlations between the SDMT and ImPACT tests, including the delayed recall components, support the overall discriminating ability of the various subcomponents of these tests to identify cognitive impairment in a MS patient group.

5.6 Synthesis of statistical indications from the study

The study was considered well-controlled for the critical influential variables that could influence neurocognitive function in a MS patient group, including age, level and quality of education, premorbid intellectual functioning, hand motor speed and depression. Therefore the overriding indication from this study of significantly impaired cognitive dysfunction in the MS patient group relative to the healthy control group cannot easily be attributed to any of those variables, and can more likely be attributed to brain impairment in the MS group. Specifically, the two most discriminatory aspects on the core ImPACT subtests were for the Reaction Time composite and the Cognitive Efficiency Index. ImPACT test scores generally, especially in the processing speed functions, were furthermore found to be correlated to the SDMT, a test which has proven utility as a screening tool with MS patients. In addition to these findings, the ImPACT Design Memory Delayed Recall subtest added compelling support for its strong

discriminatory value, thereby adding significant value to the use of the ImPACT assessment tool on the MS patient population for the identification of incipient memory dysfunction. Taken overall, therefore, all the comparative and correlational analyses indicate that ImPACT is very well suited to be utilised as a screening tool for the identification of neuropathologically induced cognitive dysfunction in MS patients.

5.7 Clinical implications

Based on the statistical results of the study outlined above, it is evident that ImPACT can be considered to be a useful screening tool for cognitive impairment in MS patients. Arising out of the investigation of this instrument in the present study, there are a number of noteworthy clinical implications.

Firstly, in following MS patients across the course of their disease process, it is likely that more than one neurocognitive assessment will be called for. Unlike the SDMT, the ImPACT test has been specifically developed with a view to repeat testing following a concussive injury. The instrument therefore has the availability of multiple forms, thus minimising practice effects when used repeatedly. On a test like the SDMT, in the absence of multiple forms, the presence of practice effects might obscure a relevant fall-off in function over time.

In order to investigate the ImPACT test for the screening of MS patients, the assessment procedure involved a carefully selected small battery that included tests to control for relevant variables that might influence outcome on this group research study. It is suggested that the battery of tests utilised in this *group* research study (see section 3.3) might be usefully applied, also, in clinical settings when doing *individual* cognitive evaluations MS patients. The total duration of the battery was approximately one hour and forty minutes, which is a reasonably manageable time frame in the individual clinical context. It is proposed that the battery has

distinct value in such a context for a number of reasons. First, it includes tests used to estimate cognitive reserve (as indexed by premorbid intelligence estimates). The battery furthermore assesses index finger dexterity and levels of depression, both factors that are important to control for with this population group. Therefore, in the individual case it will be possible to evaluate relative fall-off in function on the typically affected areas of processing speed, reaction time and cognitive efficiency, as well as delayed incidental recall compared with an estimated premorbid level of intellectual functioning. From a diagnostic point of view an evaluation of hand motor function and depression would also be useful as a means of deciding the extent to which either of these factors might be contributing to the cognitive test profile rather than organically induced dysfunction. The availability of this diagnostic clarity has implications for restorative interventions and clinical management of the individual MS patient. It is important to identify the extent to which depression is present (requiring treatment in its own right) prior to declaring an individual to be permanently cognitive impaired.

Whether or not depression is contributing to slowed processing speed in the MS patient or not, there is recent research suggesting that positive results can be obtained by focusing cognitive rehabilitation in MS patients on improving processing speed. This is especially valid during the early phase of the disease and in younger patients (Blair et al., 2016). The value of early detection and monitoring of cognitive performance, specifically with regard to processing speed, is therefore again confirmed. This is an area where ImPACT could be of great value, and particularly if used in conjunction with the adjunctive tests and depression inventory as applied in this study.

5.8 Limitations and recommendations for further research

Based on the positive results of this study it is recommended that further research on the utility of ImPACT as a screening and monitoring tool for patients with MS be undertaken. Such research should particularly address certain limitations of the study that will be delineated below.

While the study was considered well-controlled for factors that may influence results, there are a number of limiting factors that need to be taken into consideration. The sample sizes, although adequate for this circumscribed masters level thesis, in partial fulfilment of the degree only, could be increased in order to add greater statistical rigour. The composition of the MS patient group could furthermore be adjusted to take into consideration factors that may impact on a patient's vulnerability to cognitive impairment by the disease. These include factors related to the disorder itself, for example disease course and duration of disease (see section 2.2.3). Furthermore the influence of depression in conjunction with MS warrants additional investigation that was not possible in the present study. In this study, depression was on average in the "Minimal" range for both sample groups (see section 2.3.2.2 above), and there was negligible evidence of relationships of BDI-II with neurocognitive tests. Depression was therefore considered most likely to not to have had an overall influence on the neurocognitive outcomes. Pertinently the ImPACT composite scores that discriminated between the two groups did not show correlation with the BDI-II scores. Future studies with more participants might target a wider spectrum of depressed individuals in the sample, including those with moderate to severe depression, thereby facilitating a more fine analysis of the adjunctive influence of depression as part of the analysis. Various potentially important moderating factors controlled by the patient e.g., medication regimes (see section 2.3.2.5), current levels and types of mental

activity (i.e., active cognitive reserve – see section 2.2.3.4) and smoking (see section 2.2.3.6) may also be considered for investigation in future studies.

While the test battery incorporated into this test, used in conjunction with a depression screening inventory, was considered to be adequate methodologically, it might be considered a limitation that the ImPACT symptom inventory was not incorporated as part of the analysis. This was with a view to keeping the research focused on the neurocognitive aspect, particularly since the symptom items are designed with the typical post-concussive symptomology in mind. However, further studies might usefully incorporate an analysis of the symptom presentation on the ImPACT test to consider its relevance in the MS context, and it might be of value in supplementing a depression inventory.

A cross-sectional group study design as used in the present study is useful for this initial exploratory type of research. A limitation of this type of group analysis is that the outcome is revealed in terms of a group average, and the full picture in terms of the variability amongst individuals is not considered. It is important to note that the patient group in the present study included individuals who may have performed very well on the cognitive tests as indicated by the wide range of scores and relatively high standard deviations. In other words, poor cognitive performance by the patient group as a whole does not necessarily indicate that all patients with MS are cognitively impacted. Future research may consider a study design that evaluates a cohort of MS patients on an individual basis, with an investigation of individual test scores relevant to demographically equivalent norms. In terms of this individualized methodological approach it will be possible to identify the percentage of MS patients that are impaired on each functional modality, and what percentage of MS individuals are spared.

Finally, it was apparent from the study results that the two memory composite scores on the ImPACT test failed to significantly discriminate between the MS patients and the controls, and can be considered a limitation of the test in terms of its sensitivity in this context. However, the results were approaching significance, and with larger sample numbers might reveal some discriminatory ability that is being obscured in this study. Most importantly, however, is the strong discriminatory capacity of the delayed recall version of the ImPACT visual memory test that was identified in this study. Therefore, in both research and clinical settings it is essential that the result on the ImPACT Design Memory Delayed Recall subtest is monitored in addition to the core ImPACT composite scores when evaluating MS patient performance.

5.9 Final summary

This study set out to investigate the use of the ImPACT test developed in the context of concussion assessment for use as a screening tool for MS patients. In a cross-sectional comparative group design, a sample of MS patients was compared with healthy controls that were equivalent for the influential variables of age, level and quality of education, and estimated premorbid intellectual ability. The possible influence of hand motor function and depression was taken into account and considered negligible on the basis of correlational analyses with the neurocognitive test results. Taken overall, the indications are that the ImPACT test would be a useful screening tool to be used in the MS patient context, using the composite scores and the delayed visual recall component, and preferably embedded in the wider test battery employed for the purposes of the present study, in both research and individualized clinical settings. Despite some limitations of the research, it has been possible to isolate a number of noteworthy implications for future studies and clinical management for MS patients on the basis of the present research.

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Appendix A

Biographical information and pre-test screening questionnaire

Contact details

First name: _____ Surname: _____

Email: _____ DoB: _____

Education

Preprimary: School: _____ Nr of years: _____

Describe: _____

Primary: School: _____ Nr of years: _____

Repeat years ? _____ Performance: Bottom / Middle / Top

Describe: _____

High: School: _____ Nr of years: _____

Repeat years ? _____ Performance: Bottom / Middle / Top

Describe: _____

Tertiary 1: Institution: _____ Period: _____

Course ? _____ _____

Repeat years ? _____ Performance: Bottom / Middle / Top

Describe: _____

Tertiary 2: Institution: _____ Period: _____

Course ? _____ _____

	Repeat years ? _____	Performance: Bottom / Middle / Top
	Describe: _____	
Tertiary 3:	Institution: _____	Period: _____
	Course ? _____ _____	
	Repeat years ? _____	Performance: Bottom / Middle / Top
	Describe: _____	
Learning problems:	Detail: _____	ADHD: _____
	Describe: _____	

Occupation

Occupation 1:	Company: _____	Period: _____
	Position ? _____	Type: _____
	Describe: _____	
Occupation 2:	Company: _____	Period: _____
	Position ? _____	Type: _____
	Describe: _____	
Occupation 3:	Company: _____	Period: _____
	Position ? _____	Type: _____
	Describe: _____	

Medical (non-MS)

TBI / concussion:	_____	When: _____
Neurological (non-MS):	_____	Period: _____

Treated psych illness: _____ Period: _____

Alcohol abuse treatment: _____ Period: _____

Substance abuse treatment: _____ Period: _____

Non-MS meds: _____ Period: _____

Medical (MS)

1st Symptoms: _____ **1st diagnosis:** _____

Subtype and date: _____ **Steriods/relapse past month:** Yes / No

EDSS: _____ **Date EDSS:** _____

Interferon type: _____ **Since:** _____

Rapha: _____ **Since:** _____

Other Meds: _____ **Since:** _____

Other conditions

Vision problems? _____ _____

Pain: Level: _____ Normal? _____

Fatigue _____ Smoke? _____

Cognitive experiences: _____

_____

Finger Tapping Test

Handed: Right _____ Left _____ Ambidextrous_____

Right: _____ _____ Left: _____ _____

Comments: _____