The Assessment of Sustained Attention in Multiple Sclerosis:

Comparison of psychometric measures and correlates with everyday cognitive function

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This thesis has been composed by myself
and the contained herein is my own.

ABSTRACT

Multiple Sclerosis (MS) is the most common disabling neurological disease affecting young and middle-aged adults (Arnett, 2003). It is only in recent years however that the influence of cognitive impairment as a causal factor in disability in MS has been recognised. Despite clinical recognition and anecdotal reports of attentional difficulties the status of attention in MS arguably remains unclear with inconsistent findings in the research literature. The impact of sustained attention was discerned from other theoretical types of attention and the assessment of it provided the focus for study.

The Sustained Attention to Response Task (SART) was developed for using with the traumatic brain-injured population and is purported to be a sensitive and valid measure of sustained attention. The main aim of the study was to investigate whether performance on it could be replicated with an MS population. The principal hypothesis stated that there would be a significant difference between a sample of MS patients and a healthy control group across attentional measures. The Lottery and Elevator Counting subtests from the Test of Everyday Attention, the Symbol Digits Modalities Test formed the main assessment tools used. Another aim of the study was to determine how well performance on these tests predicted everyday cognitive functioning, as measured by the self and informant-reported Cognitive Failures Questionnaire.

The results demonstrated that sustained attention deficits were indeed a part of the cognitive profile in this sample of MS patients. In its current format performance on the SART was not found to be a valid measure for using with the MS population. The other three attentional tests were however able to discern a significant difference in performance between the two groups. Performance on these test were also found to significantly correlated with and hence be predictive of everyday cognitive functioning as measured by the informant-reported Cognitive Failures Questionnaire.

CONTENTS

1 INTRODUCTION TO MULTIPLE SCLEROSIS

1.1 INTRODUCTION

Multiple Sclerosis (MS) is the most common disabling neurological disease affecting young and middle-aged adults (Arnett, 2003). The prevalence of the disease combined with its progressive nature, its poorly understood pathogenesis and the complexity of the disability it causes make MS an immense challenge to patients and their families, as well as health care providers.

It is of value at the outset of this study to discern and delineate several of the key reasons why MS has proven and continues to be a challenge across various fields of interest; some of these shall be further expounded upon throughout the introduction. They include aetiology, epidemiology, diagnosis, diversity of symptoms, disease progression, treatment and management.

1.1.1 Aetiology

The oldest apparent recorded report of MS comes from the biography of St Lidwina of Schiedam written shortly after her death in 1433. In 1436 Lidwina developed walking difficulties, headaches and violent pains in her teeth following a fall whilst skating. Within a few years she was walking with difficulty and a weakness in her face caused her lip to droop on one side. Lidwina's condition deteriorated gradually

throughout the rest of her life, although with clear periods of remission (Medaer, 1979).

The first identifiable instance of MS did not occur until the early nineteenth century when the diaries of Augustus d'Este offer a twenty-six year description (1822-1848) of the symptoms now recognised to be those of MS (Firth, 1948). He delineated clear episodes of blurred vision, double vision, weakness in his legs, numbness, bladder and bowel problems and impotency, all of which cleared up without treatment and some of which recurred a few years later. By 1843 he experienced persistent symptoms including tremor and nocturnal spasms and eventually became confined to his bed for the last years of his life.

Major advances in understanding of the nervous system and the development of the science of neurology over the early and middle part of the 19th century led to a number of discoveries of the as yet unnamed condition. Such discoveries included recognition of periods of improved symptoms by Friedrich Frerich (1849), observed 'fatty corpuscles' in the scarring of nerves by Carl Rokitansky (1857), which was later to be shown to be caused by damage to the nerve covering.

In 1868 the great Parisian neurologist Jean-Martin Charcot, named 'the father of neurology', finally drew together these pieces of information and expanded on them to first identify MS as a distinctive disease, calling it 'sclerose en plaques' (Charcot, 1868). He described MS lesions in detail and reported inflammation and the loss of the covering of the nerves at these sites. He attributed symptoms to impaired conduction in the central nervous system, though with periods of remission, and

identified the so-called 'triad of symptoms,' nystagmus, slurring of speech and loss of co-ordination, as indicators of MS. Charcot's immense contribution to medicine was in tying the accurate observation of symptoms and signs of disease life with the pathological findings in the nervous system following death. It was only now after the methods of examining someone with organic disease of the nervous system had been developed that descriptions of illness going back centuries could be recognised. Indeed, with this new clarification of the condition an increasing number of cases were reported in the later decades of the nineteenth century.

Unsure of what was causing the neurological symptoms, remedies attempted by Charcot and his contemporaries included chloride, zinc sulphate, silver nitrate, strychnine, belladonna, ergot and hydrotherapy. The discovery of blood vessels in MS lesions in the 1860s led to speculative vascular theories of causation upholding that blood clots or poor circulation in the brain was the primary cause of plaques. Following the discovery of effective anticoagulants were prescribed to thin the blood but interest in this approach rapidly declined. Twenty years later MS was attributed to overexertion and treatments included bed rest and electrical stimulation (Murray, 2000).

By the early 20th Century the development of more sophisticated diagnostic and experimental assessment techniques provided scientists with the means to develop a greater understanding of the human immunological system. In turn, advances in understanding MS could follow. In 1916 James Dawson wrote a description of the inflammation around blood vessels and damage to the myelin with a clarity and thoroughness which has never been improved. So little was known about the brain's

function however that the meaning of these changes remained unknown (NMSS, 2003).

The Association for Research in Nervous and Mental Disease (ARNMD, 1922) Report of 1922 was a landmark in the understanding of MS. It brought together individuals who summarised the state of knowledge at the time and consolidated views. It led to many now classic papers on epidemiology, aetiology, pathology and clinical features of the disease. The conference on which the report was based discussed a range of possible causes including infections, environmental toxins and trauma that were being investigated at the time. Although the conference failed to derive any conclusions it did help to reject some aetiological propositions. This included a rejection of Dana's suggestion that MS was more common in skilled manual workers and in 'fat people'. Investigations into infection as a causal factor currently continue but rather than searching for an immediate cause the premise of research now looking for an infection that acts as a trigger for the later development of MS.

An examination of the genetics of MS was one of research paths developed during the 1950s. Previous family linkages of MS had been downplayed but now it was identified that there was a higher risk (approximately 1 in 40) of developing MS if a first-degree relative has it. Thus there is a genetic component but it is important to stress that MS is not hereditary and that the majority of people who develop MS have no previous family history of the condition.

The Immunologic Theory of MS

Rivers and Schwentker (1935) showed that nerve tissue, not viruses, produced the MS-like illness. By injecting myelin they knew to be virus free into laboratory animals they could induce their immune systems to attack their own myelin, producing a disease very similar to MS called experimental allergic encephalomyelitis (EAE). This finding was almost completely ignored and it was to be many years before the basic similarity of EAE and MS was understood and a connection between the immune system and MS consolidated. Variations on the EAE model are still used to assess possible changes and effects in MS and to assess the likelihood that drugs might be effective in the disease (Murray, 2000).

Research based on the immunologic theory of MS has been extensive resulting in over 7000 journal articles (Ebers, 1999). There is now firm evidence to suggest that MS is a chronic autoimmune mediated relapsing inflammatory disease affecting the central nervous system (CNS) (ffrench-Constant, 1994). Presently it provides the rational for most of the current approaches to treatment, based on modifying the immune system (Paty *et al.*, 1999). Interferons, which occur naturally in the immune system, were first identified in 1957. It was not until 1995 that this important discovery led to the licensed use of beta interferon as a treatment for MS, which aims to quieten activity in the immune system and thus slow relapse rates.

The immune system is the body's main defence against invasion by infections or other foreign bodies. It is suspected that MS is triggered via a viral or bacterial infection that has an antigen which mimics myelin, the fatty protein surrounding the axon. Through a complex process the immune system mistakes the myelin sheath for

foreign and begins to destroy it. When myelin is damaged or stripped away from an axon, the messages that pass along it are delayed or blocked. The failure of nerve messages to get through correctly means that bodily functions or processes controlled by the affected nerve pathways do not work properly. Since the CNS controls processes throughout the body and damage can take place anywhere within the CNS, this could account for the wide variance of symptoms. Although remyelination tends to occur in the earlier stages of MS, repeated attacks over time causes permanent damage and myelin is not replaced. Much of the permanent disability of MS results from such axonal destruction.

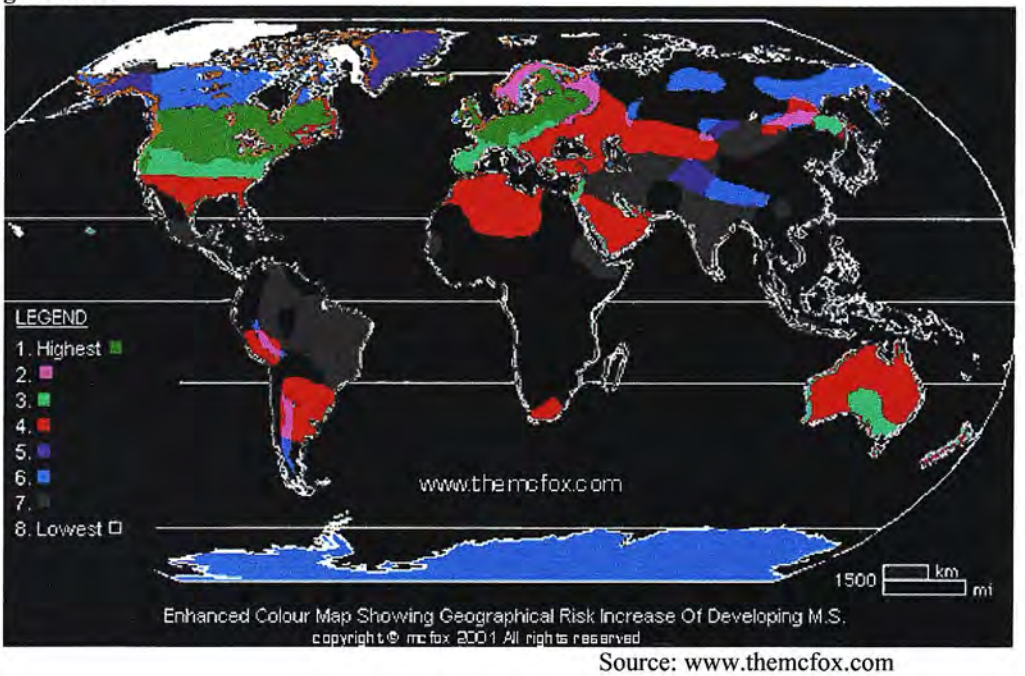
The correlation between the clinical description and the pathologic process in MS is far from precise. It is the author's opinion however that a basic comprehension of the immune system, its possible role in MS and the pathology of the disease process is important when attempting to understand the clinical description by helping to explain many of its clinical features. Therefore, a summary of this area written in lay terminology for those who do not have prior knowledge of it is imparted in Appendix 1, which also provides the reader with references for further reading.

1.1.2 Epidemiology

Studies in this area have estimated that 2.5 million people in the world have MS and that its distribution is uneven across the world. Findings from over three hundred prevalence studies (Kurtzke & Wallin, 2000) indicate that geographically MS is distributed throughout the world within three zones of high, medium, and low

frequency. Generally, MS is seen with greater frequency as the distance from the equator increases in either hemisphere, with some notable exceptions (Skegg *et al.*, 1987) as shown in figure 1.1.3. Prevalence studies for migrants from high-risk to low-risk areas indicate the age of adolescence to be critical for risk retention. Those migrating beyond age fifteen retain the risk of their birthplace; those migrating under age fifteen acquire the lower risk of their new residence. Data of this nature support the idea that MS is ordinarily acquired in early adolescence, with a lengthy 'latent' period between disease onset and symptom onset (Kurtzke & Wallin, 2000).

Figure 1.1.3



Source: www.themcfox.com

In the United Kingdom the prevalence rate is 1:800, which translates into approximately 60000 people with the disease (Compston, 1990). The most recent related study within Lothian and the Border regions (Rothwell & Charlton, 1998) report a prevalence rate of 1:500 which the authors concluded was as high as previously shown in Orkney and Shetland in 1974 (Cook, 1988) when it was reported there to be the highest prevalence world-wide. There is a recognition that some cases

of MS go undetected in life, appearing as a chance finding at post-mortem (Gilbert & Sadler, 1983). With estimates of up to twenty percent of cases falling into this category (Mackay & Hirano, 1967), it suggests that epidemiological data underestimates the true prevalence of the disease. MS is twice as common in women as in men and, although may occur at any age, onset in the late 20s and early 30s is most common. Indeed, MS accounts for around eighty per cent of residents in young disabled units across the country (Harrison, 1986). Thus the prevalence of MS alone is a significant factor in the challenge it poses.

1.1.3 Diagnosis

The central nervous system (CNS) can be divided into two parts; the brain analyses and stores information and directs the action of the body, the spinal cord passes information to the brain and is responsible for reflex actions. MS can affect many different areas in the CNS, hence the term multiple, and thus people can present with diverse patterns of neurological symptoms. Initial symptoms commonly include numbness or tingling in the limbs or weakness affecting one or more limbs, loss of vision or impaired visual acuity, diplopia, facial numbness, vertigo, dysathria, ataxia and urinary frequency and fatigue (Paty, 2000). Given the broad array and often subtle nature of neurological signs and symptoms that may be indicative of the onset of MS, the list of conditions that make up a differential diagnosis is potentially formidable (Rolak, 1996). There is no single test to determine whether someone has MS or not and thus the decision is essentially a clinical one. Providing a firm diagnosis can take many years following the onset of symptoms.

1.1.4 Disease Progression and Classification

The progression of MS symptoms and associated disability can vary markedly between patients. Some display no obvious symptoms during their lives but are found at post-mortem to have areas of scarring in their CNS that indicates MS has been present. At the other extreme, there are instances of people who rapidly develop very debilitating symptoms.

It is now recognised that there are several 'types' of MS (Lublin & Reingold, 1996). The majority of people with MS (approximately 85 per cent; Coyle, 2000) are initially diagnosed with the 'relapse-remitting' type, characterised by clearly defined disease relapses where symptoms flare up followed by periods of good or complete recovery. 'Secondary-progressive' is the next most common type (30 per cent of all MS cases; Coyle, 2000) and starts in people as relapse-remitting but over time the frequency of relapse decreases but disability increases. The next most common form is 'primary-progressive'. Accounting for approximately ten per cent of MS cases (Coyle, 2000) it is characterised by unremitting progression from onset for most patients, with occasional stabilisation for others, but with no clear relapses. 'Progressive-relapsing' is the least common form (approximately 5 per cent; Coyle, 2000) where the disease progresses from onset and where acute relapses occur from which patients may or may not fully recover.

Every attack, even subclinical attacks, cause some permanent damage to the CNS, and it is the accumulation of damage from repeated demyelinating episodes that account for most of the long-term disability. Life expectancy is shortened in MS but mortality

rates have undoubtedly declined in recent years. Weinschenker *et al.* (1989) demonstrated that the median survival time was greater than forty years with eighty-eight per cent of patients still living with the disease forty years from the initial onset of symptoms.

1.1.5 Neuropsychological Symptoms

As well as physical symptoms there is now a wide recognition that impairment of cognition is common in MS and is an important causal factor in disability, undermining people's quality of life. Cross-sectional studies have estimated the prevalence of cognitive impairment at 45 to 65 per cent (Rao, 1995). The degree of cognitive impairment correlates with occupational and social impairment independent of physical disability (Armato *et al.,* 2001). There is also some evidence to suggest that once cognitive impairments develop in MS patients they generally do not remit (Armato *et al.,* 2001). The National Institute for Clinical Excellence (NICE, 2003, p.35) clinical guidelines for MS state that 'About half of all people with MS have impaired ability to learn and remember, to plan, to concentrate and to handle information quickly. The relative high frequency of these losses is often not appreciated by clinicians, but equally must not be assumed'. Indeed, despite the negative impact on daily functioning, cognitive impairment in MS is relatively under-recognised compared to physical aspects of MS. Researchers acknowledge that there is much conflicting evidence in the field of MS and cognitive impairment (Bagert, 2002). This is the critical area of interest within this study and will be explicated in great depth latterly in this introduction.

Burnfield & Burnfield (1978) acknowledged that the emotional and relationship problems associated with MS have not always been fully appreciated by the medical profession, which has tended to concentrate on the physical aspects of this disease. Yet the psychological problems of MS often cause more suffering than physical effects. Twenty-two years later and key authors in this area are still identifying that emotional problems are still not fully appreciated and thus leading to a lack of recognition of such problems in people with MS (Feinstein, 1999; LaRocca, 2000).

For decades the emotional state of MS patients was typically considered to be euphoric, characterised by inappropriate or inadequate serenity (in view of the physical disability). Subsequent research has found that even in very disabled MS patients this type of presentation does not occur in more than ten per cent of cases (Kesselring & Klement, 2001).

It has become clear that the most common affective disorder in MS is depression (Kesselring, 1997; Minden & Schiffer, 1990) with a lifetime prevalence rate of approximately fifty per cent (Sadovnick *et al.,* 1996). This is characterised by an inability to mourn, loss of hope, pessimism, and is often associated with general loss of energy, sleep disturbance, weight loss and lack of interest. It can be difficult to differentiate which of these disturbances are due to organic disease and which are psychological reactions to MS. A quarter of all MS patients will become so markedly depressed that they require treatment by a specialist. The risk of suicide, particularly in the early stages of the disease, is markedly higher than in the general population (Kesselring & Klement, 2001).

In a review of the literature Berrios & Quemada (1990) found that in general there is a trend for those with more severe disability to be more depressed and depression to be more common in elderly patients. It was also reported that clinical anxiety tends to be more common in young people. However, it has also been argued that the presence of emotional disturbance is not related to age, sex or other demographic variables or to duration or severity of disease or the degree of disability (Dalos *et al.,* 1983). The variation of prevalence figures may find an explanation in the heterogeneous nature of MS and the potential for confusing somatic complaints of multiple sclerosis, such as fatigue and sleeplessness, with symptoms of depression. A further explanation may be found in the widely varying research methodology, selection of assessment tools and means of measuring and quantifying psychological disturbance.

For a very comprehensive review of the literature on MS and affective disorders one is directed to Feinstein (1999) who examines in detail MS with depression, bipolar affective disorder, pathological laughing and crying, and with psychosis. It is sufficient here to note the presence of affective disorders in MS and within the present context leads to an inquiry about their relationship with cognition.

This section has purported to introduce some of the features of MS that contribute to its description as a common neurological disorder producing a complex interaction of physical, psychological, social and vocational problems, displaying great variability and unfortunately tragic consequences for many people. Given the implications of MS for individuals, families, communities, as well as the broader implications for society, continued research into all aspects of MS remains intensely important.

1.2 COGNITIVE IMPAIRMENT IN MULTIPLE SCLEROSIS

Many a chapter, monograph and paper on Multiple Sclerosis (MS) begin with the observation that MS is the most common disabling neurological disease affecting young and middle-aged adults, indeed so did this introduction. Since the first clinical description of the disease 170 years ago attention has largely focused on neurological manifestations and it is only in the last fifteen years that clinicians and researchers have become more aware of the behavioural changes that may accompany MS. It is now accepted if not always clinically recognised that cognitive impairment in MS is a major cause of disability.

Descriptions of altered mentation (Stenager, 1991) in MS predate the writings of Charcot (1877) who himself perceived and wrote that MS patients may show 'marked enfeeblement of the memory, conceptions are formed slowly and intellectual and emotional facilities are blunted in their totality'. Despite this early recognition of potential cognitive difficulties in MS patients, it was the prevailing belief of clinicians throughout most of the last century that cognitive difficulties were not a significant factor in MS, and if present, generally confined to patients with severe physical disability. This section proposes to examine the literature on MS and cognitive impairment.

1.2.1 Prevalence of Cognitive Impairment

An early influential study in this area was that of Cottrell and Wilson (1926) who studied one hundred MS patients in a tertiary referral centre and observed that intellectual decline occurred in only two cases. They concluded that cognitive impairment in MS was 'minimal and negligible'. Another influential study based on clinical examinations estimated that less than five per cent of MS patients were affected by cognitive impairment (Kurtzke, 1970). Feinstein (1999) asserts that one of the reasons for clinicians failing to identify cognitive impairments can be explained by the very nature of cognitive impairment in a subcortical disease such as MS. The more observable deficits such as agnosia (loss of recognition), apraxia (impaired ability to carry out voluntary movements) and language difficulties, characteristic of cortical dementias, are for the most part absent in MS.

The introduction of Magnetic Resonance Imaging (MRI) in the early 1980s resulted in clinicians and researchers being able to visualise the brain's white matter changes with a new clarity. The search for clinical correlates thus began and today MRI and other imaging techniques have advanced the current understanding of the pathological substrate that underlies cognitive dysfunction in MS. Early studies confirmed that both the extent and the location of demyelinative lesions were related to cognitive deficits (Rao *et al.*, 1989). Magnetisation transfer imaging (MTI) and measurements of brain atrophy with MRI have now demonstrated more robust correlations with cognitive dysfunction (Edwards *et al.*, 2001) and remains the most sensitive technique available in detecting brain lesions (Brassington & Marsh, 1998). Within ten years of the advent of MRI, Kurtzke's estimate of less than five per cent was demonstrated to

have massively underestimated the extent of cognitive impairment in MS. In 1990 the National Multiple Sclerosis published their guidelines for neuropsychological research in MS (Peyser *et al.,* 1990). This contained a review of the literature that estimated that fifty-four to sixty-five per cent of MS patients were cognitively impaired. However, it was also recognised that many studies used in providing this estimate had used biased samples and were not representative of the broad spectrum of MS. For example, many studies used clinic attendees who were potentially more severely affected by MS than a community-based sample. MS patients are a heterogeneous group, comprising of individuals whose illness differs with respect to duration of illness, physical disability, frequency of disease exacerbation, disease course and site of lesions. Future research had to take into account and control for these disease and demographic-related factors.

Two influential and comparable studies followed soon after this review which took into account these factors and used community-based samples. Rao *et al.* (1991) assessed two hundred people, an MS group and a healthy control group matched with respect to age, gender and number of years of education. Both groups completed a broad neuropsychological battery of thirty-one tests which included tests of verbal intelligence, immediate, recent and remote memory, abstract reasoning, attention and concentration, language and visuospatial perception. Cognitive function was rated as impaired if scores fell below the fifth percentile scores of the normal control participants. Compared to healthy controls, the results revealed that MS patients failed significantly more tests and overall forty-three per cent of MS patients were found to be cognitively impaired. These results were replicated in a second influential study

carried out by McIntosh-Michaelis *et al.* (1991), finding forty-three per cent of MS patients cognitively impaired.

1.2.2 The relationship between cognitive impairment and other characteristics of MS

This section proposes to outline and review the literature on several aspects of MS and their relationship to cognitive impairment. These aspects include physical disability, duration of illness, disease course, affective disorders and fatigue.

Physical Disability

Research findings on the relationship between physical disability and cognitive impairment are mixed. Several studies have failed to find any relationship between the two (Peyser *et al.,* 1980; Lyon-Caen *et al.,* 1986; Ron *et al.,* 1991), in contrast, some studies have found a relationship between motor impairment and memory deficits (Huber *et al.,* 1987; Stenager *et al.,* 1989). One of the methodological criticisms of most of these studies is in the use of EDSS scale as a measure of physical disability which arguably provides a bias assessment. Whilst cognitive deficits are attributable to lesions in the cerebral hemisphere white matter, physical disability as measured by the EDSS predominantly reflects the presence of lesions in the spinal cord, posterior fossa and cerebellum, causing mainly motor effects (Feinstein, 1999).

Duration of Illness

The majority of studies conclude that there is no correlation between illness duration and cognitive impairment (Rao *et al.*, 1991; Marsh, 1980; Beatty *et al.*, 1990a). Some studies, however, have reported a positive correlation (Ron *et al.*, 1991; Grant *et al.*, 1984) but have been criticised on methodological grounds (Thompson *et al.*, 1992). In consideration of the disease course the lack of association between these two aspects makes intuitive sense, since patients with illnesses of similar duration may contrast greatly with respect to disease activity, extending from quiescent to rapidly progressive.

Disease Course

Initial studies suggested that cognitive deficits were more marked in patients with chronic-progressive as opposed to relapse-remitting MS. Heaton *et al.* (1985) found that both groups were cognitively impaired compared to a group of healthy controls but also that the chronic-progressive group were significantly more impaired than the relapse-remitting group. These differences were not related to greater sensory or motor impairment in the chronic-progressive group and persisted when the duration of the disease was controlled for. The findings of this study were validated in another study by Rao *et al.* (1987) who compared both groups and a control group on the Wisconsin Card Sort Test (test of executive functions shown to be sensitive to effects of frontal lobe lesions). The findings of this study were strengthened by a regression analysis that suggested the differences were independent of physical disability and disease duration.

Further evidence to suggest that disease course is an important predictor of cognitive impairment comes from studies confined to just one subgroup of MS. Anzola *et al.* (1990) reported a mild overall cognitive impairment in relapse-remitting patients. Rao *et al.* (1984) found that memory was significantly compromised in over fifty-per cent of those with chronic-progressive MS, and Beatty *et al.* (1988) found that seventy-five per cent of a similar population were impaired on tests of information processing speed. However, in a later study by Beatty *et al.* (1990a) contradictory findings were gained with no variable found to be a significant predictor of cognitive impairment.

More recently, longitudinal studies have shed further light on the link between disease course and cognitive impairment. Jennekens-Schinkel *et al.* (1990) demonstrated that the significant variable in determining cognitive change is not disease stage or type *per se* but lesion load on the brain, and subsequent studies have concurred (Feinstein *et al.*,1993; Hohol *et al.*,1997). These authors appeal to three aspects of disease course in arguing their findings. Firstly, whilst a chronic-progressive course may be frequently associated with more extensive brain lesions it is not invariably so. Secondly, if the lesion burden falls predominantly within the spinal cord then the disease course becomes less relevant with respect to cognition. Thirdly, findings from longitudinal studies have challenged the previously held assumption that the course of MS runs true once established.

One of the most influential papers of recent years is the meta-analysis by Thornton and Raz (1997) of thirty-six published studies of memory deficits in MS. In that review it was shown that disease course showed the strongest associations with

cognition, accounting for almost two-thirds of the variance in short-term memory and working memory but with little or no relationship to long-term memory.

Medication

In a study of ninety-two community-based MS patients one-third were found to be taking tranquillisers, seven per cent either antidepressants or neuroleptics, and two per cent morphine. Twenty-one per cent used medication that was non-sedative and only a third of patients were medication free (Stenager *et al.,* 1994). However, when tested with an array of neuropsychological tests, including the Symbol Digit Modality Test (used in this present study), no association was found between cognitive performance and the use of sedative medication. Rao *et al.* (1991) also reported a lack of specific association between medication effects and cognitive performance. In examining the effect of Interferon-beta-1b on cognitive function in MS, it was tentatively shown that this treatment had a positive effect on attention, concentration, and visuospatial learning and recall. On other cognitive domains there was no change, positively or negatively (Barak & Achiron, 2002).

Affective Disorders

It is generally recognised that depression, stress, anxiety and other emotional states can disrupt a wide variety of cognitive functions in the general population, particularly attention, concentration and memory (Lezak, 1995). It is arguably surprising therefore that numerous studies have reported no association between cognitive impairment and depression in MS patients (Clark *et al.,* 1992; Gilchrist & Creed, 1994; Moller *et al.,* 1994; Rao *et al.,* 1991). Schiffer and Caine (1991) investigated whether clinically significant depression (i.e. major depression) could

affect cognitive performance, by testing MS patients when they were depressed and, on average, seven months later when their mood state had resolved. No significant differences were found. In the widely cited meta-analysis by Thornton and Raz (1997) however, a strong correlation was found between depression and working memory deficits in ten studies but no relationship between depression and long-term memory.

Whilst the role of stress and anxiety has been considered as a potential trigger of MS onset and exacerbations (Ackerman *et al.,* 2000), its effect on cognitive impairment has not been addressed. LaRocca (2000) notes that no studies have examined this area to date, and no such studies were found when carrying out the literature search for the present study.

The role of affect on cognitive deficits in MS patients arguably remains unclear. It seems that affective disorders may have some effect but they certainly cannot explain fully the extensive cognitive changes observed in MS (Feinstein, 1999).

Fatigue

Fatigue in MS has been anecdotally associated with impaired ability to concentrate and perform intellectual tasks. Kujala *et al.* (1995) observed that, during testing, patients exhibited signs of possible fatigue and that it should therefore be controlled for in future studies. The few controlled studies carried out examining this issue have failed to establish a causal relationship between the fatigue and cognitive test performance (Caruso *et al.,* 1991; Johnson *et al.,* 1997; Paul *et al.,* 1998). The

evidence base is arguably so sparse that it would be naïve to rule out possible effects of fatigue and so minimising fatigue is normally accounted for in MS studies.

In concluding this section it seems clear from the published research that the relationship between cognitive changes and other disease characteristics varies depending on which changes and characteristics one is examining. In many instances the relationship is weak. It seems that cognitive changes can occur at any time during the course of the disease and may appear in both mildly and severely disabled patients. They can also worsen and improve during periods of relapse and remission respectively. The relationships thus provide aspects for consideration when working with and carrying out research in MS.

1.2.3 The Nature and Severity of Cognitive Change

In reviewing the literature a pattern of cognitive impairment has emerged fairly consistently and is now broadly accepted (Rao, 1986; Thornton & Raz, 1997; Brassington & Marsh, 1998; Feinstein, 1999; LaRocca, 2000). This pattern has been dubbed 'the footprints of MS', also 'the submarine problem', as well as been analogously referred to as an iceberg. All of these allude to the nature of cognitive impairment in MS and suggest that one of the reasons why cognitive impairment has been under-recognised is that the type of problems are typically hidden to the casual observer and perhaps even to neurological examination. Hence the value of neuropsychological assessment.

Drawing from the aforementioned reviews this section intends to discern the pattern of cognitive impairment in MS, and with reference to the literature demonstrate the extent of the evidence.

General Intelligence

Cross sectional studies of intellectual functioning have found that whilst most MS patients have IQs within the average range there are small, consistent differences between them and normal control participants (Rao, 1986). Longitudinal studies have demonstrated a small but significant decline in intellectual functions over time. When measuring intellectual functioning most researchers have used versions of the Wechsler Adult Intelligence Scales (WAIS) (Wechsler, 1955) and it is of significance that the small differences reported indicative of decline in IQ are confined to scores on the performance (non verbal) subscales with verbal scores remaining unchanged (Penman, 1991; Rao, 1986).

More recent analysis of MS patients score profiles on the WAIS suggest that that there is considerable individual variation in the I.Q. scores of MS patients (Rao *et al.*,1991; Feinstein *et al.*,1997), Studies that focus on group scores may therefore obscure significant declines in individual patients. They also highlight that there are more subtle indications of impairment on the digit-span subtest on the verbal subscale. The digit-span is a composite score of recalling digits forwards and backwards and MS patients as a group perform normally on this test. However, when the forward and backward components are analysed separately, relative deficits on the backward recall are observed.

Several studies have addressed quantitative changes in IQ from estimated or actual pre morbid levels. Canter (1951) administered the Army General Classification Test to twenty-three men who had developed MS after joining the military. The men had all completed the same test prior to enrolment and thus came about a unique opportunity of comparing directly a premorbid performance with that post-MS onset, a study which remains the only one of its kind. The test-retest period was up to four years and a significant drop of 13.5 I.Q. points was found. Ron *et al.*, (1991) in a study using premorbid estimates of I.Q. found a significant decline in MS patients compared with a group of disabled control subjects who had neurological disorders sparing the brain.

It is of interest to note that of the major reviews in this area referenced at the commencement of this section none state how prevalent decline in intellectual functioning is. Arnett (2003) states that intellectual functioning is affected significantly in about twenty per cent of patients. Unfortunately he does not specifically reference where this figure is derived from, nor does he delineate how it was obtained. The considerable debate surrounding the value of an overall measurement of general intellectual functioning *per se*, the variability of lesion location in MS and the fact that most MS patients score within the broad normal range has led most neuropsychologists to focus on specific functions rather than global measures (LaRocca, 2000).

Memory

Numerous studies during the past twenty years have examined the nature of memory in patients with MS and demonstrated impaired ability on several types of tasks

(Beatty, 1993; DeLucca *et al.*, 1994; Rao, 1993). Overall prevalence rates across many studies confirm that memory impairments are the most common cognitive deficits in MS, being evident in forty to sixty per cent of patients (Rao *et al.*,1993; Thoronton & Raz, 1997). In a study that randomly selected patients from the community and inpatient neurological service, thirty per cent of MS patients were severely impaired, thirty per cent had moderate impairment while only forty per cent had little or no impairment (Mindon *et al.*, 1990).

Short term memory (STM) (also referred to as working, immediate or primary memory) is the system responsible for the immediate recall of small amounts of verbal and non-verbal information. STM may be divided into two broad sub-components, namely the phonological loop and the visuo-spatial sketchpad. The former is responsible for the recollection of words, numbers and melodies, while the latter is confined to the recall of spatial information (Baddely, 1986).

With respect to MS the amount of information held in STM has been found to be normal (Rao *et al.*, 1984; Heaton *et al*,1985) or mildly impaired (Lyon-Caen *et al.*, 1986; Kujala *et al.*, 1996) in relation to healthy controls. Despite mixed evidence, reviewers seem to agree that MS patients have the ability to store information in STM and access it successfully (Brassington & Marsh, 1998; Thornton & Raz, 1997). Both components are controlled by a central executive that regulates the distribution of limited attentional resources and controls cognitive processing when novel tasks are presented or existing habits need to be over-ridden (Baddely, 1986). D'Esposito *et al.* (1996) postulated that any impairments of STM might relate to a dysfunction within

the central executive that fails to provide sufficient attentional resources to process multiple tasks simultaneously.

Long-term memory (LTM) (also referred to as secondary memory) refers to memory that exceeds the capacity for primary memory and can be divided into episodic and semantic memory. It is in this aspect of memory that research has found most impairment within the MS population (Rao *et al.,* 1991; Caine *et al.,* 1986; Beatty *et al.,* 1988). The impairments found are more obvious on tests of free recall as opposed to recognition (cued recall) and this leads to the suggestion that the problem is principally one of retrieval and not the encoding of new information (Armstrong *et al.,* 1996; Coolidge *et al.,* 1996; Rao, 1986).

In contrast with research implying an impaired retrieval mechanism, other researchers have suggested that impaired encoding of information into LTM underlies the memory deficits observed in testing. DeLucca *et al.* (1994) found that MS patients required significantly more trials to initially learn a task, relative to healthy controls, but once learnt, did not differ from controls in delayed recall of verbal material, nor in recognition memory performance. The authors also argue that studies purporting to identify deficient retrieval processes as central to observed memory impairment fail to control for the amount of information initially acquired during learning. In an influential review of memory impairment in MS Thornton and Raz (1997) conclude that deficits in LTM cannot be explained purely by a retrieval deficit and that encoding problems offer partial explanation.

The term 'implicit memory' or 'procedural memory' refers to memory that is not reliant on conscious recall and encompasses motor skills, conditioning and priming. The consensus of opinion is that MS patients perform normally on this aspect (Beatty *et al.*, 1990b; Grafman *et al.*, 1991). Another aspect of LTM is 'remote memory' which is a clinical term relating to recall for information stored prior to an amnesic episode. Findings are inconsistent on this aspect, some results have been equivocal (Beatty & Monson, 1991) and some have noted abnormalities (Rao *et al.*, 1991).

Attention

Arnett (2003) notes that attentional functioning and information processing speed are difficult concepts to separate since the former is necessary for performing any speeded task. Considered together Arnett asserts that around twenty to twenty-five per cent of MS patients have problems in this cognitive area. Some researchers and reviewers treat them separately but note the relationship (Brassington & Marsh, 1998; LaRocca, 2000) and others discuss them together (Feinstein, 1999). Since this is the area of most area of most relevance to this study a detailed dilution of these aspects will be provided latterly in the introduction. For the purposes of clarity in this section the literature on attention and information processing speed will be examined individually.

Once again the issue of definition of terminology arises when one considers 'attention' as a cognitive domain. A clear and universally accepted definition of attention has not yet appeared in the literature. Attention, it seems, refers to several different capacities or processes that are related aspects of how the organism becomes receptive to stimuli and how it may begin processing incoming or attended-to

excitation (Lezak, 1995). Typically different theoretical types of attention, for example, simple, selective, sustained, divided, and alternating attention, are separated out when discussing attentional impairments. These will be discussed in detail latterly in this introduction but it is of interest to note that despite the recognition of and literature on the complexity of attentional processes, most of the comprehensive reviews of cognitive function in MS fail to address it. Brassington & Marsh (1998) is one of the most well known, respected and often cited review articles on the neuropsychological aspects of MS, yet little space is afforded to attention.

In 1990 Sullivan *et al.* surveyed 1180 people with MS and of the thirty-eight per cent who reported cognitive difficulties in at least one area of cognitive processing, twenty-two per cent of these reported difficulties with attention and twenty-three per cent reported memory problems. Lezak *et al.* (1990) found that MS patients often confuse attention and memory processes and interpret attentional impairments as memory problems.

The role of attention in presenting memory problems initially provided the theoretical rationale for assessing attention in MS. Several studies have suggested that some memory deficits may be secondary to a primary impairment of attention (Thornton & Raz, 1997; DeLuca *et al.*, 1994). Coolidge *et al.* (1996) reported memory performance to be significantly affected by the presence of interference in comparison with a non-interference learning condition. Grafman *et al.* (1991) investigated effortful and automatic processing in MS and control participants and reported equivalent performance on automatic processes, but reported MS participants to be significantly more impaired than controls on measures of effortful processing.

Several studies investigating attention in MS have concluded that there is little or no trace of impairment when compared to controls. Beatty *et al.* (1995) reported that digit span (subtest of WAIS) performance to be in the average range for patients with MS although scores were significantly lower than matched controls. DeLuca *et al.* (1995) also reported no difference on digit span when comparing MS and control groups. Whilst digit span is a commonly used measure of attention in clinical practice research findings using it have been inconsistent (Beatty *et al.*, 1996). Mild deficits have been reported in some studies (Huber *et al.*, 1987; Lyon-Caen *et al.*, 1986) but not in others (Heaton *et al.*, 1985; Rao *et al.*, 1984). Kujala *et al.*(1995) in trying to account for processing speed found that a cognitively impaired MS group performed slower on all tests of attention but did not differ from controls in the error scores. Beatty *et al.* (1995) state that because there does not appear to be any orderly relationship between illness variables such as disease type, disease duration or disability status and patterns of performance on measures of attention and immediate memory, most researchers have concluded that attention is intact or at most mildly impaired.

These findings are in stark contrast with other studies that identify attentional impairment as significant in this population. Callanan *et al.* (1989) investigated a range of functions and reported impairments of attention as the most prominent cognitive abnormality in MS. In a study comparing MS with Alzheimer's groups the former were found to be more impaired on measures of visual and auditory sustained attention. It has been demonstrated that MS patients show a greater decrement than controls in the performance of dual condition tasks than single condition tasks (D'Esposito *et al.*, 1996). Foong and Ron (1999) claim that attention may be the most

vulnerable area of cognitive impairment in early MS. Furthermore, McCarthy *et al.* (2001) state that most studies reporting attentional impairment in MS indicate that sustained attention is the most impaired. Beatty *et al.* (1995) also suggested that MS patients suffer from mild generalised difficulty in maintaining concentration as well as a more specific impairment in regulatory systems that allocate limited attentional resources among multiple stimulus tasks.

It has been consistently found (Beatty *et al.*, 1988; DeLuca *et al.*, 1994; Litvan *et al.*, 1988) that MS patients exhibit deficits on the oral version of the Symbol Digit Modalities Test (SDMT) (Smith, 1982) and on the Paced Auditory Serial Addition Test (PASAT) (Gronwall, 1977). In MS literature, impairments on these tasks have usually been attributed to slowing of information processing, but in both clinical and experimental work with other patient populations the SDMT and the PASAT are often considered to be measures of attention (van Zomeren & Brouwer, 1994). This arguably provides further evidence of attentional impairment in MS.

Such contrasting positions inevitably beg the question as to the explanation behind such disparity in results and McCarthy *et al.* (2001) suggest three main reasons. Firstly, the variability which typifies the disease trajectory in MS, as described throughout this introduction section. The controversy concerning attentional deficits in MS may be due to the differences in the MS population, especially in the cognitive status of patients. The cognitive performance of MS patients has typically been studied by assessing the performance of one cognitively heterogeneous patient group or by classifying the patients into subgroups according to physical disability, disease onset, and duration. As noted earlier such disease variables have arguably no

correlation with cognitive profiles and so is arguably not a sensible way of analysing cognitive performance. Kujala *et al.* (1995) suggest that studying cognition in MS should be completed according to a subdivision of those who are and those who are not cognitively impaired.

The second plausible explanation for reported performance anomalies is the diversity of measures used to assess attention. As previously noted attention seems to refer to several different capacities and it is arguably important that these differences are taken into consideration when assessing. If different tests are measuring different attentional capacities then failure to delineate which aspect of attention is being measured can plausibly explain in part the different conclusions drawn across various studies.

The third credible reason for the diversity of findings within the literature on MS and attention is the lack of psychometric validity for many of the standard attentional paradigms used in assessment. The very nature of attention makes it not easily observable and requires analysis of a person carrying out a task, which inevitably involves other abilities which, given the diverse symptoms of MS, may also be impaired thus rendering results difficult to interpret. A related aspect of this is the notion of ecological validity and such tests. Ecological validity is defined as the '...functional and predictive relationship between the client's performance on a set of neuropsychological tests and the client's behaviour in a variety of real-world settings' (Ginsberg *et al.*, 1995). Multiple sclerosis is a disease for which ecological validity may be especially pertinent. The relatively early onset of MS within the life span and the long duration of its course means that patients typically experience many years of

functional disability. Therefore, enhanced ability to predict functional disability in MS is important for treatment planning and rehabilitation.

These three aspects will be considered further in section 1.3 when the subject of attention is examined comprehensively. The relative space given to attentional processes in the major reviews of cognitive functioning in MS arguably highlights the paucity of literature on this domain. Based on the limited literature the status of attention in MS currently remains unclear.

Information Processing Speed

Charcot observed that slowness of thinking was one of the hallmarks of mentation in MS patients. In reviewing the evidence Brassington & Marsh (1998) conclude that slowed information processing is a major feature of the cognitive profile in MS. They note that whilst the impairment is exaggerated by additional physical impairments, it appears to have a cognitive basis. Once again however there are inconsistencies amongst the literature, as well as very different means of measurement.

Using the Sternberg Memory Scanning test in a matched control study Rao *et al.* (1989) found that patients with MS exhibited a significantly slower overall reaction time. Mouthrop and Nudelman (cited in Brassington & Marsh, 1998, pp.53) also found evidence of slowed mental speed in thirty-three patients that could not be attributable to motor impairment or lower global functioning. However, Litvan *et al.* (1988) found no such differences when using the Sternberg test.

An indirect measure of assessing information processing speed is via the use of simple and choice reaction time tests. The former gives a measure of basic psychomotor speed and the latter introduces an element of choice and hence problem solving. By subtracting the two a measure of pure cognitive speed can be obtained. Research using this method has found impairment in MS patients relative to controls (Elsass & Zeeberg, 1983; Jennekens-Schinkel *et al.,* 1988). However, it was also found that increasing the complexity of the task did not result in further slowing in the MS group compared to the controls which the hypothesis would imply. Feinstein (1999) suggests that the approach lacks sensitivity and is affected by deficits in vigilance or the ability to sustain attention.

The Paced Auditory Serial Addition Test (PASAT) (Gronwall & Wrightson, 1974) is purported to be a sensitive measure of impairment in processing speed. Abnormalities have been reported using this test in many studies (Litivan *et al.,*1988; Rao *et al.,* 1991; DeLuca *et al.,* 1994; Feinstein *et al.,* 1993). Diamond *et al.* (1997) also found such impairment but concluded that as the performance of the patients with MS was characterised by a stable decline as opposed to a steadily increasing decline, processing speed may not be the critical determinant in accounting for the poor performance.

Executive Functioning

Executive functions incorporate cognitive abilities such as abstract and conceptual reasoning, problem-solving, cognitive flexibility, and planning (Baddelly, 1986). Canter (1951) stated that his observation of the most striking psychological loss in MS is that of the ability to analyse and synthesise abstract problems. Arnett (2003)

asserts that fifteen to twenty per cent of MS patients show substantial difficulties in these domains. Such deficits may reveal themselves in terms of daily planning, verbal disinhibition, and tangential speech, as well as problems in organising ideas and shifting appropriately from one conversation topic to another.

Early studies (e.g. Parsons *et al.*, 1957) which demonstrated deficits in executive functioning have been replicated more recently, most often using the Wisconsin Card Sort Test (WCST) (revised version, Heaton, 1981). The WCST has proved effective in differentiating MS patients from healthy controls (Heaton *et al.*, 1985; Beatty *et al.*, 1989b; Mendozzi *et al.*, 1993) and disabled patients without brain involvement (Rao *et al.*, 1987; Ron *et al.*, 1991). These results are supported by studies using other neuropsychological tests, including the Raven's Progressive Matrices (Rao *et al.*, 1991) and the Category Test (Heaton *et al.*, 1985; Rao *et al.*, 1991). Using assessments of specific aspects of executive function Beatty and Monson (1996) concluded that problem solving difficulties reflect an impairment in identifying concepts rather than perseveration. In an earlier study (Beatty & Monson, 1994) sequencing, another aspect of executive functioning, was commonly found to be impaired in patients with frontal lobe lesions.

It has been hypothesised that the executive functions become impaired when connections between the frontal lobes and subcortical structures are disrupted (Bronston & Cummings, 2001). In reviewing the data from 'frontal' tests such as the WCST and the Controlled Oral Word Association Test (COWAT) (Benton & Hamsher, 1976), Feinstein (1999) concludes however that at present there is an

inability to localise brain regions responsible for particular functions with any degree of anatomical precision.

Language

Two forms of expressive language disorders have been commonly reported. Aphasias are rare in MS (Achiron *et al.,* 1992) but mild confrontation-naming difficulties are sometimes seen. This is often referred to as the 'tip of the tongue' phenomenon, and is when the individual cannot think of a specific word but feels as though it is on the tip of their tongue. A common complaint that seems to combine elements of memory loss and slowed processing is a decrease in verbal fluency (Beatty *et al.,* 1989). Rao *et al.* (1991) report that twenty to twenty-five per cent of all patients have substantial problems on verbal fluency tasks.

Visiospatial Deficits

Visuospatial skills are a challenge to assess accurately in MS because primary sensory abilities (visual) and motor functions are often impaired, which makes it difficult to evaluate the role of higher cognitive processes. Despite this it is believed that a variety of visuospatial skills may be impaired in MS and affect approximately ten to twenty per cent (Rao *et al.,* 1991). Angle matching and face recognition are two of the most commonly reported problems but they may also include many other specific skills like discriminating right/left and giving directions.

This section has purported to discern the nature of cognitive impairment most common in MS based on a body of research literature. Having outlined the 'footprints' of cognitive dysfunction in MS it is also important to reiterate the fact

that because MS lesions are generally widely dispersed in the brain almost any brain function can be affected.

1.3 ATTENTION

> *'Everybody knows what attention is. It is the taking possession by the mind, in clear and vivid form, of one out of what may seem several simultaneously possible objects or trains of thought. Focalisation, concentration of consciousness are of its essence'.*
>
> William James, 1880.

Open many cognitive psychology or neuropsychology books that address the subject of attention and these now famous words of William James will often serve as the introduction. Following this is usually an inevitable counter that whilst it is true that the term 'attention' is one that everyone recognises and is in common usage, a definition is far from clear.

Attention has long posed a major challenge for psychologists. As with many fundamental topics in neuropsychology, the role of attention in mental life has been known for many years. Augustine of Hippo (350-430) made comment on the phenomenology of attention that resemble present day intuitions about how different events in the world attract our attention (cited in Neumann, 1971). Research on attention underwent a major revival in the 1950s arguably due in part to advances in technology when it became easier to study and analyse unobservable mental processes (Pashler, 1998).

Developments in neuroscience during the 1980s (Hillyard & Picton, 1987; Raichle, 1983) opened the study of higher cognition to physiological analysis, and revealed a system of anatomical areas that appear to be central to the selection of information for conscious processing. Since then the scientific analysis of attention disorders, particularly following brain damage, has rapidly expanded. Increasingly it is being

reported that attention plays an important role in recovery from brain injury, as both a function in its own right and a facilitator to other abilities. It is this potential for rehabilitation of attention to in turn aid other cognitive functioning rehabilitation which has led to 'cautious optimism' (Manly *et al.,* 2002) within the area of rehabilitation.

Providing a concise overview of the history and development of attention theories is a considerable challenge as the breadth of writing is vast. Posner & Peterson (1990) acknowledge that the study of attention has been plagued with vagueness and thus can quickly become confusing. Hence the author proposes to address only the following areas in this next section. Firstly, to provide a theoretical basis for the study of disparate functions of attention. Secondly, to examine the methods of and the issues surrounding, the assessment of attention. And thirdly, to introduce the specific concept of sustained attention. Whilst the focus of this study is multiple sclerosis most of the research carried out in this area pertains to head injury and stroke. Attempts will be made to focus on the implications for multiple sclerosis in section 1.4.

1.3.1 A theoretical basis for disparate attention functions

One of the major contributing factors in failing to reach agreement on the definition of the term 'attention' is that it seems to refer to several but interrelated abilities. Allport (1993) states that there is no uniform function to which we can attribute everything that has been labelled as attention. On this there is at least agreement, attention is not a unitary concept.

A brief delineation of one of the most common definitions of attention serves to demonstrate the variety of functions. van Zomeren (2003) writes that attention is a state of processing system that is optimally tuned in terms of selectivity and intensity. These dimensions are readily comprehensible in the spotlight metaphor: attention can be directed like a spotlight to illuminate a certain object, while the intensity may vary (Yantis, 1998). This intuitively makes sense, when one needs to read something complicated one selectively focuses intensely on it, discriminating it from other internal and external stimuli like memories or people talking or music, that one may respond to. Taking the analogy further, the spotlight needs energy to run on and some people have the ability to concentrate on complicated tasks for longer than others do thus ability to sustain the spotlight is another function of attention. Many people do other activities simultaneously to studying, for example listen to music or cook dinner, and thus the spotlight may be shared into several parts, hence the term divided attention. There are several criticisms of the spotlight analogy (Yantis, 1988; Erikson & Murphy, 1987; Remington & Pierce, 1984) but it serves here to illustrate the point that attention is not a unitary concept.

Recognition of these different functions are easily described in terms of everyday examples but have proved harder to delineate in terms of taxonomy. Several different taxonomies have been proposed, some of them psychological (Mirsky *et al.*, 1991; van Zomeren & Brower, 1994) and others based on neuroanatomy (Mesulam, 1985; Posner and Peterson, 1990). From these taxonomies two caveats arguably emerge for neuropsychologists (van Zomeren & Spikeman, 2003). Firstly, statements about the attention of a patient should always be qualified in terms of a specific task and situation. This is illustrated in the example of someone who has sufficient attention to

hold a social conversation but not to drive a car through rush hour traffic. Secondly, the assessment of attention cannot be limited to performance on a single test.

One of the fundamental difficulties of assessing attention is the fact that it is not readily observable. Assessing attention often requires asking a person to carry out a task, but inevitably that task involves other perceptual, cognitive and motor factors. One method of resolving this problem has been to infer attention from the systematic variation in performance under different attentional conditions. It is from such methods, in conjunction with neuroimaging techniques, that a clearer account of the capacities, limitations and neural basis of attention has developed (Manly *et al.*, 2002).

Anatomical Localisation of Attention Processes

The issue of anatomical localisation of mental functions has always played a prominent role in neuropsychology. Historically the discussion has shifted from the extremes of phrenology (Gall & Spurzheim, 1808) and equipotentiality (Lashly, 1950) towards contemporary emphasis on functional networks (Fuster, 2003). Today, complex mental activities are generally not viewed as the product of single centres nor of the brain in general. Rather, such functions are thought to depend on the integrated activity of large-scale networks, in which each component delivers a specific contribution (Fernandez-Duque & Posner, 2001).

In line with the popular view in cognitive psychology that attention is inherently spatial, many models describe visual attention as controlled by spatial processing structures, typically located in frontal and parietal areas. Now a highly influential

paper, Posner and Peterson's (1990) review of the area elucidated three key principles of attentional function, under their taxonomy. Since this is a key aspect of the present study these principles are quoted below.

> *'First...the attention system of the brain is anatomically separate from the data processing systems that perform operations on specific inputs even when attention is oriented elsewhere. In this sense, the attention system is like other sensory and motor systems. It interacts with other parts of the brain but maintains its own identity. Second, attention is carried out by a network of anatomical areas. It is neither the property of a single centre, nor a general function of the brain operating as a whole...Third, the areas involved in attention carry out different functions and these specific computations can be specified in cognitive terms'.* (Posner & Peterson, 1990, p.26.)

Posner and Peterson go on to propose and argue for a broad, three-way division of voluntary attention mediated by semi-independent networks. Evidence from Positron Emission Topography (PET) and more recently functional Magnetic Resonance Imaging (fMRI) studies in normal individuals have provided the strongest support for the argument that attention is fractionated into different systems, and that these systems have distinct neuroanatomical bases. These three subdivisions of attention along with the supporting evidence will now be concisely presented.

Orienting Attention

Orienting attention (or spatial attention) refers to the capacity to move attention within space. Within the visual domain we usually achieve orienting by directing our eyes toward the location of interest (overt orienting), but it is also possible to assign priority to an area of the visual field without moving the eyes (covert orienting). A very simple way to examine covert orienting of attention is to require the person to maintain fixation while processing a visual event peripheral to the current fixation.

Many studies of normal experimental participants have demonstrated that information is processed more efficiently at an attended peripheral location than at other locations equally distant from the fixation point (Posner & Peterson, 1990). The anatomical networks involved are similar for overt and covert orienting (Corbetta, 1998). PET and fMRI studies show that orienting attention activates the precentral gyrus of the frontal lobe and areas in the parietal lobe (Corbetta, 1998; Rizzolatti & Craighero, 1998). This same network is also activated during attention tasks that are unrelated to eye movements thus non-spatial, for example, a shift in attention between to dimensions (e.g. colour and shape) (Le *et al.,* 1998) and in time (Coull & Nobre, 1998).

Selective attention

Selective attention refers to the ability to use stored information efficiently to sort out relevant from irrelevant information. On a daily basis people are constantly bombarded with stimuli of all sorts; an ever-changing visual scene, numerous sounds, tastes, smells and things we touch. Yet despite this mass of stimuli one can focus in on what we want to, and this is selective attention. The areas usually activated include the anterior cingulate and supplementary motor area, the orbitofrontal cortex, the dorsolateral prefrontal cortex, and portions of the basal ganglia and the thalamus (Bench *et al.,* 1993; Bush *et al.,* 1998; Posner & DiGirolamo, 1998).

Sustained attention

Sustained attention refers to the ability to self-maintain an alert or vigilant state. Two types of task have been used to study this area, warning tasks and continuous performance tasks. Posner and Peterson (1990) propose that the right frontal and

parietal areas are important in both tasks. PET and fMRI studies support this and show that sustained attention increases activation in the fronto-parietal system, even when no stimulus occurs (Pardo *et al.*, 1991). Auditory vigilance tasks also activate right frontal areas (Belin *et al.*, 1998; Cohen *et al.*, 1988). Furthermore, activation in those areas decreases as a function of time, and this decrement correlates with some measures of vigilance decrement (Paus *et al.*, 1997). Fernandez-Duque & Posner (2001) conclude that such findings reveal the existence of a sustained attention system that is anatomically separate from the data-processing systems.

Upholding this theoretical model has residual implications for neuropsychologists (Manly & Robertson, 2003). An anatomical and functional division between attention systems and other sensory, motor, or cognitive systems implies that damage to that area can produce a deficit that is exclusively or predominantly attentional in nature. Furthermore, the demarcation of attentional functions within discrete regions leads to the contention that impairment can occur in one attention function whilst another may be relatively intact. Such evidence contributes to the argument that attention cannot be assessed using one test and that to carry out an adequate assessment one must necessarily use tasks that place differential demands on different forms of attention.

1.3.2 Assessment of Attention

It has already been highlighted that assessing attention can only be achieved by asking a patient to complete some form of verbal, visual or motor task. This can make assessment difficult particular if a patient has other sensory, motor or cognitive

impairments. A further problem is that asking people to do a task often involves more that one aspect of attention. For example, a time score obtained in a visual search task may reflect both the speed of processing of visual information and higher-order aspects of attention such as strategy and flexibility (van Zomeren & Spikman, 2003).

Observation is the oldest approach to the assessment of attention, which has the advantage of being able to offer a naturalistic perspective and insight therefore into how any impairment manifests itself in an individuals life. Rating scales and questionnaires help to standardise observation and can capture the perspectives of several interested parties on the same dimensions e.g. patient, relative, and care staff. The results of rating scales should not, however, be used in isolation. Patients, particularly those with attentional or executive impairments, may not be ideally placed to report problems due to lack of insight or awareness (Wilson *et al.,* 1997; Burgess *et al.,* 1998). The reports of others may be influenced by positive or negative halo effects, from low inter-rater reliability, and from insensitivity to small changes in function. Furthermore, given the confusion of terminology surrounding this area it may be difficult for observers to identify specific behaviours intended by the authors of the rating scale in question.

Despite these difficulties, such measures play an important role in building up a detailed picture of potential attentional impairments, and in monitoring function over time. Two of the most frequently recommended measures (Manly *et al.,* 2002; van Zomeren & Spikman, 2003) with known reliability and validity are the Cognitive Failures Questionnaire (Broadbent *et al.,* 1982) and the Rating Scale of Attentional Behaviour (Ponsford & Kinsella, 1991).

The other means of assessing attention is through the use of available neuropsychological tests. Spikman *et al.* (2001) reviewed the construct validity of commonly used tests and found two main factors, speed (or processing capacity) and control (working memory). As noted earlier in this introduction, these two concepts are not completely independent and van Zomeren & Spikman (2003) identifies that the distinction and relationship between them offers a useful method for categorising tests of attention into three levels.

The first level is termed the 'operational' level and is where speed is the main factor while control is minimal. Essentially the aim is to measure speed of processing and this is achieved by making the task so simple that errors are extremely rare. Examples of such tests are the Trailmaking A, colour naming in the Stroop Test, and also Digit Symbols from the Wechsler Adult Intelligence Scales (Spreen & Strauss. 1998).

The second level is termed the 'tactical' level and is where participants have to work speedily but more control is required in order to prevent errors. At this level there is a distinction made between focused and divided attention. In the former, participants must respond to information selectively i.e. when there are distractors. Such tests include Trailmaking B, or Map Search and Telephone Search from the Test of Everyday Attention. The concept of divided attention refers to tasks that require more than one type of response. Examples of such tests include the Paced Auditory Serial Addition Task (PASAT), the Test for Attentional Performance (TAP), and the Test of Everyday Attention.

The third level is termed the 'strategic' level and is where time pressure is minimal but participants have to find their own approach to performing a task. This inevitably leads to a paradox since strategy can be deployed only in an unstructured situation, but a test requires standardisation and hence structure. However, examples include the Wisconsin Card Sorting Task, the Six Elements Test from the Behavioural Assessment of the Dysexecutive Syndrome (BADS), and the Tower of London test.

The advantage of psychometric tests over rating scales is that they can allow for a quantitative assessment of performance on a task under controlled conditions. They also provide the opportunity for repeat testing to address changes in function over time, plus they allow the assessor to compare performance with normative data. However, it has become clear that they represent only a snapshot of abilities under particular conditions and their usefulness as a predictor of performance in everyday life remains a topic of current debate (Manly *et al.*, 2002; Robertson *et al.*, 1997). The predictive validity of various attentional variables has not been clearly established (Denes *et al.*, 1982; Fullerton *et al.*, 1986). As well as carrying implications for the validity of neuropsychological assessment of attention, it also gives rise to how one evaluates the effectiveness of rehabilitative interventions. Most of the tests outlined do require attentional capacities in order to complete them, however, they often rely heavily on working memory, episodic memory and low-level visuospatial abilities without teasing apart the underlying components of attention. Furthermore, these traditional neuropsychological tests predate current theoretical models of attention such has been previously outlined and thus there is arguably an ambiguous relationship between tests and subsystems of attention.

1.3.3 Sustained Attention

'Constant attention wears the active mind,
Blots out our pow'rs, and leaves a blank behind'
Charles Churchill

As a proem to the topic of sustained attention two vignettes are provided below.

Vignette one.

'In the 1993 British Football Association Cup Final, a defender for Brighton and Hove Albion failed to prevent a Manchester United player from passing him and scoring a goal. Together with the scorer and the Manchester supporters, the Brighton player raised his arms in an unmistakable gesture of celebration. It was only when his arms were fully raised in triumph that he and several thousand supporters became aware of his error and he returned his arms slowly to his side' (Manly, 1999, p.661).

Vignette two.

'The time is World War II. A British patrol plane flies over the Bay of Biscay. Inside, an observer peers at a speckled, flickering radar screen looking for a tell-tale spot of light or 'blip' that will signal the presence of an enemy submarine on the surface of the sea. The observer has been on watch for a little over thirty minutes and nothing much has happened. Perhaps this mission, like so many others, will be fruitless. Suddenly, the 'blip' appears but the observer makes no response. The 'blip' appears a few more times. Still the observer fails to respond. Evidently, the signal has gone undetected and, as a result, so has the submarine' (Warm, 1984, p.1).

To be absentminded is to be inattentive to ongoing activity, to lose track of current aims and to become distracted from intended thought by conspicuous but (currently) irrelevant stimuli. Everyone has experienced doing something that they did not intend as a result of attention failure and these types of mistakes are referred to as actions slips. The consequences of such action slips are often unimportant, for example, when one puts milk into a requested black coffee, or when one misses the turn for a road that one knows well but rarely uses. However, as in the second vignette outlined above the consequences of an action slip can be critically portentous, indeed, Reason (1979) found that most British civil aircraft accidents were the result of pilot action slips rather than errors of judgement. There is considerable normal variation in absentmindedness (Broadbent *et al.,* 1982) but any damage to the brain, particularly to the prefrontal cortex, has been found to increase the likelihood that such errors will be made (Luria, 1966; Shallice & Burgess, 1991). Thus whilst the occasional mishap of minor consequence may not effect the everyday lives of most people, if such action slips become a frequent occurrence in someone's life it can lead to considerable disability, practically and emotionally.

It has been argued that such impairments arise out of damage to a Supervisory Attentional System (SAS) (Norman & Shallice, 1986; Robertson *et al.,* 1997). In this system the majority of actions are carried out by routines which do not require conscious intervention. However, when these routine activities will not suffice, the SAS intervenes and initiates an appropriate response. Typically the SAS would be called into action in tasks which, because of their novelty, require planning, or where a strong response tendency needs to be inhibited because it is inappropriate. For example, if everyone in the office at work has milk and two sugars in their tea and

drinks several cups a day, making one for a rare guest who does not have either milk or sugar requires the SAS. It also means that via such a system complex but routine activities can be performed appropriately in a rather automatic, stimulus driven fashion (Norman & Shallice, 1986).

Stuss *et al.* (1995) and Robertson *et al.* (1997) have applied the concepts of Supervisory Attentional Control to the process of sustaining attention. The task of driving a car provides a useful example for understanding their application. If one is driving on an icy road and the wheels of ones car is skidding, the environmental factors are sufficient to make sure that you are alert. Contrast this with driving down the empty M8 late at night, mile after mile of monotony, and this presents a different challenge where one has to actively maintain alertness. In essence, a distinction is made between the capacity for endogenous modulation of alertness (self-sustained attention) with exogenously controlled alertness, which is governed by factors such as novelty, salience and stimulus change (Robertson *et al.*, 1997).

This position leads to a definition of sustained attention as the 'ability to self-sustain mindful, conscious processing of stimuli whose repetitive, non-arousing qualities would otherwise lead to habituation and distraction to other stimuli' (p.747 Robertson *et al.*, 1997). Thus in tasks of sustained attention, minimising environmental factors will maximise the assessment of people's capacity to self-sustain attentional control on the task. Traditionally this has often been achieved by making tasks long-lasting, repetitive, undemanding, and requiring only rare responses to signals that are given without forewarning (e.g. signal detection of a rare stimulus); such tasks are known as vigilance tasks (Warm, 1984). Using vigilance tasks Mackworth (1968) concluded

that often people performed perfectly on such tasks and that errors, when they did occur, were observed only after relatively long periods of time, usually more than thirty minutes.

There has been considerable interest for many years in the development of such tasks because of the fundamental importance of sustained attention in every application of behaviour. Monitoring functions have become integral elements in many civilian and military tasks in which inspection, quality control and surveillance activities are involved. For example, concern was raised about how long people could maintain their search for defective products on a product assembly line. In another example, the explosion at the Chernobyl nuclear power station in 1986, with its devastating consequences, was analysed by Reason (1990) and found to be due to a complex sequence of action slips. With so many possible applications and residual implications, the ability to assess for impairment of sustained attention remains an important aim in many circles.

Despite this importance and interest the search for attentional performance measures that correlate with everyday action slips in the normal population have yielded little success (Rabitt & Abson, 1990). Indeed, in Mackworth's (1968) studies normal adult controls typically performed normally for over an hour before making the kind of errors that one would identify as impairment of sustained impairment. When using brain injured patients with observed attention deficits, minimal decrements were only observed when the visual stimuli were heavily perceptually degraded (Parasuraman *et al.,* 1991). From a neuropsychological perspective there is therefore a lack of adequate characterisation of the attention deficits shown by such patients with various

forms of brain damage, due in part it is argued to inadequate measures of sustained attention (Robertson *et al.*, 1997).

Robertson *et al.* (1997) made an important distinction that has led to considerable development across the area of sustained attention research and proffered a reason why it has been difficult to develop sensitive measures of sustained attention. In typical vigilance tests participants have to respond to rare targets, thus most of the time on task involves not making any response, which therefore provides time to detect a target and make an appropriate response. Furthermore the presentation of a rare target can itself 'catch' a person's attention. Robertson *et al.* contrast this with a situation in which people must inhibit responding to rare stimuli. In such circumstances most of the task involves doing something and then the person interrupts the usual behaviour upon presentation of target stimuli. They provide the example of a train driver who keeps driving, which they consider behaviour requiring sustained attention though it subjectively may feel automatic, and must respond to warning signals by interrupting the normal behaviour.

It was, in part, from making this distinction that the aforementioned authors developed the Sustained Attention to Response Task (SART) (Robertson *et al.*, 1997), and the findings that have critically motivated this present study. The SART is a simple test in which a random series of digits from 1 to 9 are presented at regular intervals on a computer screen. The participant's task is to press a button after each number is presented except when the number 3 occurs. This apparently simple task becomes more difficult over time and a few participants last more than four minutes before pressing the button after a number 3 is presented. Evidence from a number of

studies have supported the position that the SART is a measure of sustained attention; the inability to withhold responding on this task is due to poor sustained attention (Manly *et al.* 1999).

The main findings of the Roberston *et al.* (1997) study were as follows. SART performance discriminated brain-injured patients from matched healthy controls, whereas a more conventional perceptually based vigilance task did not. In normal healthy controls, SART performance significantly correlated with self-reports of attentional and other 'cognitive failures' in everyday life, as well as with informant reports of such failures. SART performance was strongly correlated with informant reports of daily life attentional failures in the brain-injured group. No attentional measures were correlated with self-reported problems with attention in the brain-injured group. In summary the authors conclude that the SART is a sensitive measure of sustained attention impairment and predicts self-reported and informant-reported attentional failures in normals, and informant-reported attentional failures in brain-injured participants.

Subsequent research using the SART has not only supported these initial findings but along with brain imaging techniques provided evidence for the anatomical and functional division between attention subsystems (Robertson & Garavan, 2004). O'Connor *et al.* (2004) demonstrated that performance on the SART, when compared with a rest period, showed precisely the right frontoparietal activation that earlier studies (e.g. Posner & Peterson, 1990) would predict.

Two further studies have shown that performance on the SART can be improved by presenting non-informative auditory arousing tones randomly during task performance (Manly *et al.,* 2002; Manly *et al.,* 2004). It was hypothesised that these exogenous stimuli externally activated sustained attention thus reducing the demands on the endogenous components of the system. Using fMRi once again it was demonstrated that presenting such stimuli did eliminate the right frontal activation, however, it was also demonstrated that it did not eliminate the right parietal activation. This led the authors to hypothesise that the parietal component may be a common pathway for both endogenous and exogenous routes, while the right frontal element may be particularly linked to endogenous activation.

The Test of Everyday Attention (TEA) (1994) is a battery of attention tests which aims to assess attention from the same theoretical position as the SART, that of several independent attention systems serving different functions in everyday behaviour. Developed by Robertson *et al* (1994) the TEA was the first test battery to attempt to measure different types of attention and provides norm-referenced scores on tests that are sensitive to selective attention, sustained attention and attentional switching. It is marked by its attempt to demonstrate ecological validity which it creates by choosing tasks that closely resemble daily life situations.

Ecological validity is defined as the '...functional and predictive relationship between a person's performance on a set on neuropsychological tests and the person's behaviour in a variety of real-world settings' (Ginsberg *et al.,* 1995). Ecological validity is particularly pertinent in MS due to the early onset and relatively preserved

life span, where prediction of functional disability is likely to be beneficial for treatment planning and rehabilitation.

Despite being over ten years old, the TEA has only been used in one study using MS participants thus far (Higginson *et al,* 2000). This study did not however use the two subtests of sustained attention within the battery, Elevator counting and Lottery. They were excluded because it was assumed that they were too simple, resulting in a ceiling effect and hence not sensitive enough for use with the MS population. This remains an assumption and there is no evidence in the literature to suggest that MS patients would score normally on it. In the Elevator Counting subtest participants are aurally presented with a series of unevenly distributed tones within a given period, which represent floors in a building and their task is to count the floors. In the Lottery test participants must listen to a series of lottery numbers given in the format of two numbers followed three letters and identify all those lottery numbers ending in '55' by stating the two letters that prefix those numbers.

In the light of such paucity of detailed knowledge about cognitive impairment in MS it is surprising that an established clinical battery like the TEA has not been utilised in research. Early research into other populations (stroke and closed head injury) (Robertson *et al.,* 1994) found differing attentional profiles and thus provides evidence for the theoretical position of several independent attention systems. The Lottery and Elevator Counting subtests are deemed to be specific tests of sustained attention and ecologically valid and therefore arguably require to be considered in the examination of sustained attention in the MS population.

Arguably the most important motivation in developing tests of sustained attention within the public or military domain has been to eliminate as far as possible the likelihood of failures in sustained attention. Attempts to sustain attention have involved such methods as limiting time on task, taking away time pressures, and building in external cueing e.g. visual or verbal stimuli. Such techniques have been identified as important and significantly effective in the rehabilitation of sustained attention impairments in people with brain damage (Robertson *et al.,* 1995). The TEA and the SART in particular have provided the area of sustained attention research with a new motivation and incentive; not only may it provide a sensitive measure of sustained attention that is predictive of everyday attentional and cognitive problems, it also may have a role in rehabilitation.

In summary, this chapter has proposed to elucidate the argument for disparate anatomical and functional sub-systems of attention. In doing so it has been suggested that current attention measures do not adequately characterise the nature of attentional impairment. It has purported to outline the nature of sustained attention, the importance of it within daily living, its role in rehabilitation, and some of the historical difficulties in assessing it. Recent developments by Robertson and his colleagues, related mainly to the brain-injured population, have opened up the field afresh for new research into this area across various populations.

1.4 SUMMARY

Multiple Sclerosis is the most common disabling neurological disease affecting young and middle-aged adults. The prevalence of the disease combined with its progressive nature, its poorly understood pathogenesis and its variation in presentation contributes to make it a considerable individual and society challenge. Cognitive dysfunction is a major contributing cause of disability with memory, learning, attention and information processing being the most common deficits reported. Few authors though have specifically considered the impact of cognitive disturbance on everyday activities of patients with MS, perhaps the most critical question from a patients perspective (Amato, 1995).

Despite clinical recognition and anecdotal reports of attentional difficulties the status of attention in MS arguably remains unclear with inconsistent research findings. Some authors have concluded that attention is intact or at most mildly impaired in MS, others have found that MS patients exhibit deficits on specific tests of attention (particularly sustained attention) and some have gone on to suggest that attention may be the most vulnerable area of cognitive impairment in early MS. The disparity in the literature has arguably arisen in part due to poor methodology and also in part to the nature and quality of assessment tools used for measuring attention.

Evidence has been provided to support a current theoretical understanding of attention which asserts that there are at least three different subdivisions of attention mediated by semi-independent networks, orienting, selective and sustained attention. The major implications of such a model hold that damage to a particular area of the brain can

produce a deficit that is exclusively or predominantly attentional in nature, and that impairment can occur in one attention function whilst another may remain relatively intact. The residual implication for neuropsychology is that current tests of attention used in clinical practice are arguably inadequate to characterise attention profiles. Whilst highlighting the problems of current assessment measures it also implies that more than one test is required to achieve examination fully of attention.

Based on work with brain injured patients Robertson *et al.* have recently developed tests, underpinned by the theoretical argument of anatomical subdivisions of attention, which are designed to measure different types of attention. The Test of Everyday Attention (TEA) is the first normed and non-computerised test battery assessing the selective, switching and sustained subdivisions of attention, and deemed to be ecologically valid. The Sustained Attention to Response Task (SART) is not available commercially yet but it is purported to be a sensitive measure of attention and the first test to correlate with and hence be a predictor of informant observed attentional slips in everyday life. Its sensitivity to mild impairment may be particularly useful in MS since it has been suggested that any impairment that exists in this population will be mild.

The most widely used test of attention for use with MS patients is the Symbol Digit Modalities Test (SDMT). It is currently the recommended test because it can be completed aurally thus circumventing any motor impairments and has been shown to be a sensitive measure within this population and predictive of everyday function (Beatty & Goodkin,1990; Feinstein, 1993, 1999). However, poor performance on the SDMT has often been attributed to information processing speed rather than attention

impairment. Disparity over interpretation along with the fact that it is a single test, suggests that such a measure alone is not sufficient to screen for attentional problems in MS and certainly not adequate to characterise attentional impairment fully. Self-report measures have also been used to help assess attention but it has been argued that people with attentional problems may lack insight or awareness.

The sustained attention subtests in the TEA and the SART which do aim to characterise one of the subdivisions of attention, that of sustained attention, and which claim to be ecologically valid have not as yet been used in any research studies with MS patients. If the findings using the SART with a traumatic brain injury population can be replicated with an MS group this may have notable implications.

From a patient's perspective the most important question arguably is what will the impact of sustained attention dysfunction be on everyday activities and in purporting to be a measure predictive of everyday functioning the SART may help provide an answer.

The sensitivity of the SART to mild sustained attention problems in traumatic brain injury may for the first time provide the means of accurately assessing such problems in MS, thus improving knowledge of this area. Not only that but accurate measurement of sustained attention ability (as well as other subdivisions of attention) may help with rehabilitation two-fold. Firstly, investigations of computer assisted retraining of attentional impairments in patients with multiple sclerosis have found that such rehabilitation is more effective when the subdivisions of attention are trained separately. It may be that the SART can be used to test such potential rehabilitation

regimes. Secondly, the SART itself could be used to train people to improve their performance on attentional tasks. Manly *et al.* (1999) found that a training program which warned participants of potential errors improved subsequent scores on SART. If this effect transfers to 'real-life' tasks then this technique could help train people who have impaired attention.

An interesting avenue of cognition in MS research comes from Spilich *et al.* (2002) who assert that neurodegenerative diseases such as MS that separate into different diagnostic categories may well first manifest their divergence by subtle but measurable changes in cognitive processes. It is further held that changes in cognitive processes may appear long before frank physical symptoms. If different types of MS could be identified, by changes in cognitive processes, earlier than currently possible this could improve the efficacy of current treatments by commencing them as early as possible. Such a possibility may seem far off but arguably it must start with the development of appropriate, reliable, valid and sensitive assessment measures, and the SART may offer the first steps to achieving this.

1.5 AIMS

The main aim of this study is to investigate whether the SART is a sensitive and valid measure of sustained attention that can be effectively used with MS patients and hence whether performance on it can replicate those with a brain injured population. This involves examining the correlations between performance on it and everyday functioning, as well as other attentional tests. The study also aims to determine if people with MS are more likely to be significantly impaired in sustained attention ability than normal controls, something that arguably remains unclear in the literature. A further aim is to investigate performance on the current recommended test of attention for MS patients, the SDMT, with tests of sustained attention.

1.6 HYPOTHESES

I. The MS group will perform significantly poorer than the healthy control group across all the neuropsychological tests of attention carried out.

II. There will be a significant difference* between the MS group and the healthy control group on the informant-reported Cognitive Failures Questionnaire (CFQ).

III. There will be a significant difference* between self-reported and informant-reported CFQ scores in the MS group.

IV. Performance on the Sustained Attention to Response Task (SART) will significantly correlate with everyday cognitive failures, as measured by the informant-reported Cognitive Failures Questionnaire (informant CFQ).

V. The SART will correlate with the informant CFQ more strongly than the other attentional tests (Lottery, Elevator Counting, and SDMT), and hence be a stronger predictor of everyday cognitive functioning.

VI. Performance on the SART will correlate with other measures of sustained attention

* bi-directional hypotheses

2 METHODOLOGY

2.1 Design

The study design involved is an independent samples design, with an experimental group of patients with multiple sclerosis, and a control group of healthy volunteers

2.2 Participants (Including Inclusion & Exclusion Criteria)

The experimental group comprised twenty-six individual participants who had a diagnosis of multiple sclerosis provided by a consultant. Participants were obtained from a combination of community-based and hospital-based populations and no distinction was made between MS types (although this is recorded in the results section). They were identified as suitable and initially approached for participation in the study by Consultant Neurologists, MS nurses, outpatient team staff, and inpatient team staff. These staff members were located in three hospital sites, the Astley Ainslie, the Western General and the Liberton Hospital.

The control group comprised of thirty-one individual healthy volunteers. They were recruited through informants, church and amateur music groups.

Inclusion Criteria

The principal inclusion criteria for the experimental group were a definite diagnosis of multiple sclerosis and also having been identified as having cognitive problems by health staff. The reason for this latter criterion, as discussed in the introduction (section 1.2.3), is that disease variables have arguably no correlation with cognitive profiles hence it is not a sensible way analysing cognitive performance. This leads Kujala *et al.* (1995) to suggest that when studying cognition in MS one should subdivide those who are cognitively impaired from those who are not. People were identified as having cognitive problems on the basis of neurological examination and observation from staff involved with the patient, rather than formal assessment by a neuropsychologist, since this approach is more the norm in clinical practice in Lothian.

Exclusion Criteria

Potential participants, both for experimental and control groups, were excluded from the study if they:

- had a history of drug or alcohol misuse
- had a recorded history of a major psychiatric illness based on DSM-IV-TR diagnostic criterion (American Psychiatric Association, 2000)
- had a previous brain trauma requiring hospitalisation and treatment
- had dementia
- had a nervous system disorder (other than MS for experimental group)
- were currently involved in other medical or psychological research
- did not speak fluent English, or were aphasic.
- had visual, aural or motor impairments that would hinder performance of tasks

Specific only to the experimental group was the additional exclusion criterion that if the person was in an active phase of MS then they would not be considered suitable for participation.

Those identifying potential participants (aforementioned staff) were provided with information on the minimum level required. The participants were also tested prior to carrying out the assessments by checking that they could competently see and hear similar examples of the stimuli, as well as comfortably press the mouse quickly for a period of five seconds. No potential participants identified as suitable by health staff were subsequently deemed unsuitable to participate following a brief check of these aspects.

Demographic Information

The age, gender, and length of formal education (years) of each participant was taken. In the experimental group the type of MS and the period (years) since diagnosis was also taken. The participant's General Practitioner's name and address was taken so that a letter outlining their participation could be sent, in line with ethical standards.

2.3 Measures

The measures used in this study will now be discerned, along with the evidence supporting their use.

2.3.1 Wechsler Test of Adult Reading (WTAR) (The Psychological Corporation, a Harcourt Assessment Company, 2000).

A measurement of estimated pre-morbid intelligence was obtained using the WTAR. Participants are presented with fifty irregularly pronounced written words and asked to read them aloud, responses are correct if pronounced correctly. The correct number of responses is used to estimate premorbid intelligence.

The methodology for the development of the WTAR is directly associated with that of the National Adult Reading Test (NART) (Nelson, 1991) but developed and co-normed with the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) (Wechsler, 1997a) and the Wechsler Memory Scale-Third Edition (Wechsler, 1997b). Like other such tests the WTAR is based on the understanding that reading recognition is relatively stable in the presence of cognitive declines associated with normal ageing or brain insult, although it is not impervious to the effects of significant intellectual impairments (Spreen & Strauss, 1998).

The test is normed for the United Kingdom population from ages 16-80. Using a clinical group of eighty-three, consisting of five disparate neurological disorders, and a similar sized control group, it was concluded that there was no significant difference

for all the groups except the group with moderate Alzheimer's dementia. With regard to validity, the WTAR correlates most highly with other measures of reading recognition, as well as correlating highly with measures of verbal intelligence. With regard to reliability the WTAR has excellent internal consistency and temporal stability, based on a sample size of 331 (WTAR, 2001).

It is acknowledged that tests such as the WTAR and NART, are only one method of several in estimating premorbid intelligence (Vanderploeg, 1994). Other methods include the collection of historical data reflecting past achievements, best performance across a range of tests, and demographic information. It is well documented that all approaches to estimating premorbid intelligence are subject to error (Stebbinss & Wilson, 1998). Obtaining an estimate of premorbid intelligence is of considerable importance in assessing for possible changes in functioning and hence such methods are tolerated within clinical practice and research.

A particular criticism of the WTAR and NART is that the assumption that reading irregular words is less vulnerable to brain damage has been shown to be false (Grober & Sliwinski, 1991; Ryan & Paulo, 1992). Morris *et al.* (2005) assert that given the heterogeneity of injury severity and lesion location it is arguably sensible to infer that scores obtained on tests such as the WTAR and NART may be impaired and hence premorbid IQs underestimated, for a notable proportion of people affected by brain injury. The WTAR also has been criticised for not being able to predict premorbidly high functioning individuals. For example, a 47-year-old who achieves a perfect score, obtains a scaled score of 120, however, this only converts to a full scale IQ of 114, thus rendering it impossible to obtain a superior IQ. This creates a difficulty in interpreting a drop from high premorbid functioning.

Despite such criticisms there are clear reasons justifying the use of the WTAR in this present study. Firstly, it only takes minutes to administer and does provide a broad measure sufficient for matching samples. Secondly, such a method is commonly used across research and within clinical practice. Thirdly, there are no other methods that are free of criticism, and is being used in conjunction with the demographic information of age and years in education. Fourthly, it has been selected over the NART because it is the only test co-normed with the Wechsler intelligence and memory scales, and this makes it more likely to be of use in future more expanded studies in this area. Finally, one would hope any 'inaccuracies' in WTAR measurement would be counterbalanced across experimental and control groups. The estimates of premorbid IQ are complimented by demographic information, as is common place in clinical practice.

2.3.2 Sustained Attention to Response Task (SART) (Robertson, I., Manly, T., Andrade, J., Baddely, B. T., & Yiend, J. (1997) 'Oops!': Performance correlates of everyday attention failures in traumatic brain injured and normal subjects. *Neuropsychologia, vol.35, 6,* 747-758).

The SART is considered to be a test of sustained attention. The SART was administered on a DELL laptop computer (screen size 220x290mm) running on E-Prime psychology software (Schneider *et al.,* 2002). In the task single digits from 1-9 are presented serially within a random sequence, and in a randomly selected size (between 12 and 29mm), at the centre of the computer screen. Each digit is presented for 250ms followed by a ring with a diagonal cross mask of 900ms duration, giving a

digit onset to digit onset interval of 1150ms. The digit '3' was nominated in advance as the 'no-go' target and was presented at a probability of 1/9. See Appendix 3 for an illustration of the number sizes and masking symbol.

The participants were asked to press for each number as quickly as possible, with the exception of the nominated digit '3'. The requirement for both speed of response and accuracy of withholding responses was stressed. Responses were made by pressing on a single click Mac mouse, which with no buttons acts as a large sensitive switch. 18 practice trails were given (containing two target items) before 225 test trials were presented. No restrictions were placed on participants regarding either their positioning relative to the screen or on how they pressed the mouse (finger choice, hand etc.). The aforementioned version and procedure is in accordance with the original SART study using brain injured and healthy control participants (Robertson *et al.*, 1997).

The SART is not yet commercially available as a published formal test. Thus most of the research published on this test are written by the authors themselves (Roberson *et al.*, 1997; Manly *et al.*, 1999; Manly *et al.*, 2002; Dockree *et al.*, 2004; Fassbender *et al.*, 2004) and hence may be open to the criticism of bias. However, response to that research has been on the whole very positive and promising. van Zomeren & Spikman (2003) state that it 'might turn out to be quite useful'. Lund (2001) states that the initial findings suggest that the SART may have a number of practical uses.
Reliability was tested by administering the procedure on two occasions over a period of a week using twenty-five normal subjects, and obtained a Pearson correlation of 0.76 showing that performance on this test is stable over time. It has been

demonstrated that the SART shows stronger relationships with measures of sustained attention than other types of attention. Reliability and validity have not been fully established and there are no available norms. Hence, the need for a control group and the independent samples design.

There are four main reasons for its inclusion in this study. Firstly, the authors maintain that it is a sensitive measure of sustained attention and as such may elicit mild deficits of attention that may have been missed in previous studies examining attentional problems in MS. Secondly, to the authors' knowledge, it is also the first laboratory test on which performance predicts attentional slips in everyday life as discussed in section 1.3.3. Thirdly, it is one of only a few new tests that are designed to measure a specific sub-division of attention, thus in-keeping with theoretical developments in models of attention. Lastly, since this promising test is currently not available formally, it represents an early and unique opportunity to apply it in the MS population.

2.3.3 The Test of Everyday Attention (TEA) – Elevator Counting & Lottery subtests (Robertson, I. H., Ward, T., Ridgeway, V., & Nimmo-Smith, I. (1994). *The Test of Everyday Attention.* Suffolk, UK, Thames Valley Test Company).

The TEA is a battery of attention tests which aims to measure different types of attention and provides norm-referenced scores on tests that are sensitive to selective attention, sustained attention and attentional switching.

It is a standardised test based on a normative sample of 154 normal volunteers. The predictive validity of the TEA has yet to be established, but it has been found to have high test-retest reliability and to correlate with other measures of attention (Robertson *et al.*, 1996). van Zomeren & Spikman (2003) conclude that the reliability of all the subtests is good with the exception of Telephone Search while Counting. The validity of the TEA has been studied in cerebrovascular accident (CVA) and head-injured patients and can be judged as satisfactory.

The TEA contains two subtests considered to be tests of sustained attention and both are described below.

Elevator Counting

This subtest is based on the procedure devised by Wilkins *et al.* (1987) and developed by Broks *et al.* (1988). Participants are asked to pretend they are in an elevator whose floor-indicator is not functioning. They have to establish which 'floor' they have arrived at by counting a series of tape-presented tones (Robertson *et al.*, 1994). There are seven presentations and a score of one for each correctly counted presentation is given. Due to the low ceiling effect there are no scaled scores or percentiles. None of the normative sample made more than one error (Robertson *et al.*, 1994) and thus scoring 7/7 is normal, 6/7 is doubtful, and 5/7 is considered definitely abnormal.

Lottery

In this subtest, the participants have to listen for their winning number, which they know ends in '55'. To do this, they must listen to a series of audio-tape-presented numbers of the form 'BC143', 'LD967', etc. The task is to write down the two letters

preceding all numbers ending in 55, of which there are ten. The total lottery numbers read out are not provided but the test lasts for 10minutes and 14 seconds, hence a winning number is a relatively rare occurrence. In this study, participants were asked simply to say out loud the two letters that they heard thereby circumventing motor difficulties common in MS. Scaled-score equivalents for each of four age bands are provided.

There are three main reasons for including Elevator Counting and Lottery subtests in the present study. Firstly, they are part of a test battery that remains the most widely recognised and clinically used assessment battery of attentional tests. Secondly, they are established tests of sustained attention that have not been applied to the MS population. Thirdly, they are potentially viable tests for this population in particular because they do not require the participant to use motor skills, an aspect that can sometimes confound test performance in this population.

Both these subtests are usually presented on audio-tape. For the purposes of practicality, the two subtests were put onto compact disc so that it could be played on the laptop using additional multimedia speakers. Since testing was mainly carried out in peoples homes this reduced the amount of equipment needing transferred.

2.3.4 **The Symbol Digit Modalities Test (SDMT)** (Smith, A. (1982). *Symbol Digit Modalities Test. Manual (revised).* Western Psychological Services, Los Angeles).

The Symbol Digit Modalities Test is similar to Wechsler's Digit Symbol subtest, except that the participant responds with numbers instead of symbols so that a verbal response is possible, making it a preferable test for using with MS patients. Participants are provided with a key consisting of nine symbols, each of which is paired with a single digit ranging from one to nine. Below the key is a random list of the symbols without the numbers. The participant is instructed to respond verbally to each of the symbols, in order, with the correct number paired with it in the key. The key is kept in sight and participants are given ninety seconds to complete as many items as possible.

Norms are provided for adults aged 18-78 years, and scores indicated to be suggestive of cerebral dysfunction provided. Smith (1982) claims that the SDMT is the most sensitive measure of cerebral integrity. The test has been shown to be sensitive to brain insults in adults, and impaired performance has been associated with a number of conditions (Spreen & Strauss, 1998), including MS (Tsolaki *et al.*, 1994). Performance also appears to be related to real-world functioning (Stenager *et al.*, 1994).

The difficulty regarding what the SDMT measures has been discussed in the previous section, indeed, it is in part because of these difficulties that the present study has developed. It primarily assesses the scanning and tracking of attention. It is included

in the present study for two reasons. Firstly, the SDMT is the most widely used measure of attention in MS, perhaps due to the fact that it can be completed orally (Feinstein, 1999). Secondly, it remains the current recommended test of attention in MS (van Zomeren & Spikman 2003) because it is considered to be a sensitive test to attentional impairment in MS (Beatty & Goodkin, 1990; De Luca *et al.,* 1994) and hence a useful screening measure.

2.3.5 Cognitive Failures Questionnaire (CFQ) (Broadbent, D. E., Cooper, P. F., FitzGerald, P., & Parkes, K. R. (1982). The Cognitive Failures Questionnaire (CFQ) and its correlates. *British Journal of Clinical Psychology, 21*, 1-16).

The Cognitive Failures Questionnaire (see Appendix 4) is a 25-item self-report inventory that inquires about a person's problems with memory, perception, and motor function over the past 6 months (e.g., "Do you bump into people?" "Do you find you forget appointments?"). All questions are worded in the same direction. The response format uses a 5-point Likert-type scale (0 = never, 4 = always). Scores for the CFQ can range from 0 to 100. All items on the CFQ are positively correlated with each other. Cronbach's alpha for the CFQ was found to be .91, and the CFQ has a test-retest reliability of .82 over a 2-month interval (Vom Hofe, Mainemarre, & Vannier, 1998). The CFQ has been correlated with several other measures: Slips of Action Form A (r = .57) and Form B (r = .58), Absent-Mindedness Questionnaire (r = .62). Everyday Memory Questionnaire (r = -.64), Short Inventory of Memory Experiences (r = .74; Martin, 1983), Absentmindedness in Shops Questionnaire (r = .46; Reason &

Lucas, 1984), and Cognitive Interference Questionnaire (r = .34; Yates, Hannell, & Lippett, 1985).

Some reservations were made with regard to using this questionnaire due to the fact that three of the twenty-five questions contain a motor component, for example, question 24 asks 'do you drop things?'. Motor and vision difficulties are common symptoms in MS and this may lead an over-estimation of cognitive difficulties.

Despite this there were three reasons why it was selected in the present study. Firstly, an examination of similar scales of cognitive functioning was found to contain more questions with motor components. Secondly, the original SART study (Robertson *et al.*, 1997) used the CFQ with a brain injured sample where multiple impairments are also common. The study provided empirical evidence that the CFQ is related to a behavioural measure of sustained attention. Thirdly, the CFQ has the benefit of having a version for an informant (e.g. relative or carer) to fill in about the participant which potentially provides additional information on the participant's awareness into any impairments that may exist.

2.3.6 Hospital Anxiety and Depression Scale (HADS) (Zigmund, A. S., & Snaith, R. D. (1983). The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandanavica, 67,* 361-370).

The HADS is a questionnaire commonly used as a screening measure of levels of Anxiety and Depression. It comprises statements which the patient rates based on

their experience over the past week. The 14 statements are relevant to either generalised anxiety or depression, the latter being largely (but not entirely) composed of reflections of the state of anhedonia (inability to enjoy oneself or take pleasure in everyday things enjoyed normally).

Each question has 4 possible responses. Responses are scored on a scale from 3 to 0. The maximum score is therefore 21 for depression and 21 for anxiety. A score of 11 or higher indicates the probable presence of the mood disorder with a score of 8 to 10 being just suggestive of the presence of the respective state. The two subscales, anxiety and depression, have been found to be independent measures. In its current form the HADS results are divided into four ranges: normal (0-7), mild (8-10), moderate (11-15) and severe (16-21). In providing UK normative data (n=1792) Crawford *et al.* (2001) suggests that the cut off scores for caseness should be 10 or 11 for both anxiety and depression, rather than the 8 prescribed in the original study.

There is no consensus on how anxiety and depression is best measured in MS but the HADS has been shown to be useful (Feinstein *et al.,* 1999) and it was initially developed for use with neurological patients. One of the main strengths of the HADS is that it endeavours to avoid somatic items that might reflect physical health problems rather than truly reflecting anxiety or depression. For this reason it was selected over other common questionnaires of mood e.g. Becks Depression Inventory 2nd Edition (BDI-II) (Beck *et al.,* 1996) and Becks Anxiety Inventory (Beck & Steer, 1993). The HADS cannot be considered to be a diagnostically valid measure of mood, however, it remains commonly used in clinical practice and provides a useful and quick screening measure.

2.4 Procedure

2.4.1 Recruitment

Experimental Group (MS)

Meetings were held with the various Consultant Neurologists, MS nurses, rehabilitation teams and out-patient neurology teams that were to be involved in the recruitment of participants. The criterion for suitable participants and the expected role of staff was provided and discussed fully, as well as other practical issues. A member of staff approached individuals identified as suitable and briefly outlined the nature and purpose of the research, and gave a detailed information sheet (see Appendix 2). It was emphasised that the individual was not obliged to participate and that they could withdraw from the study at any time with no consequences. They were then given two weeks to consider consenting to their contact details being passed on the researcher. If an individual gave consent to being contacted the researcher then made contact to discuss the study in more depth. If the individual was in agreement to participate arrangements were then made for a suitable time and venue, with participants given the option of having the appointment at their local hospital or at their own home.

Control Group

The researcher approached a church group and two amateur musical groups and gave a five-minute talk on the nature and purpose of the study, as well as an invitation to contact the researcher should they wish to find out more and/or agree to participate. Latterly, in an attempt to match age and gender, individual hospital staff were

approached individually. None of the controls were familiar with the neuropsychological tests used in the study. All were provided with an information sheet slightly adapted to that for the MS group but containing similar information (see Appendix 2). Appointments were made on an individual basis and again participants were given the option of carrying out the assessment at their home or at the Astley Ainslie Hospital.

2.4.2 Testing

The following procedure took place for all participants:

- Brief overview of purpose and nature of testing, including a further opportunity to ask questions
- If participation agreed then appropriate consent forms were signed (see Appendix 2)
- Demographic information was obtained by questioning
- A brief screening was carried out to check that participants were able to see and hear sufficiently for the tasks, as well as sufficiently press the mouse.
- The five neuropsychological tests were then administrated (WTAR, SART, Elevator Counting, Lottery, SDMT). The participants had been randomly allocated (by virtue of appointment date) to one of six presentation orders. This was done in order to control for fatigue.
- The HADS and the CFQ were completed either by the participant themselves, or by the researcher doing the writing.

- The informant CFQ was to be completed by someone who knew the participant well. The participant elected this known person. In some cases the elected known person was available at the same appointment and thus was directly handed the informant CFQ along with the relevant information sheet and consent form (see Appendix 2). They were given the opportunity to complete it there and then, or provided with a stamped-addressed-envelope (SAE) to return it in as soon as possible. In other cases where the elected known person was not available, the informant CFQ, information sheet and SAE were put into a sealed envelope and either given to the participant to pass on to their elected known person, or posted out directly to them.

Sessions lasted for between forty and sixty minutes.

2.5 Ethical Considerations

The main ethical issue regards the fact that this study may highlight possible impairments of sustained attention in MS without provision for practically helping such people. Although there is no individual feedback to participants regarding their individual results, if the finding of the research suggests that sustained attention is a problem in MS then participants may wonder if they have such deficits and desire help for this.

It was made clear to potential participants before consent was given, that:

- It would not be possible to report or feedback individual findings
- There would be no direct individual benefits to participation
- Each participant would however receive a brief written summary of the outcomes of the research along with details of how they could access the full thesis through the University of Edinburgh
- If participation resulted in concern regarding attention problems then individuals would be told to speak to their consultant and that participation would not provide any treatment input at all.
- Their General Practitioner would be informed of their participation in the research but again no results would be passed on to them.

It was deemed that the risk of distress through participation would be minimal if at all. When people are given a diagnosis of MS they are made aware that they may develop cognitive difficulties such as attention and memory problems. This is rarely assessed for within normal clinical treatment of MS. Being made aware that they may have attention problems is not new to people who have a diagnosis of MS.

In this study all the results collected were recorded anonymously by using numbers rather than names thus confidentiality was provided. The results were stored on an Edinburgh University laptop computer and kept in a locked cabinet.

Lothian Research Ethics Committee granted the study full ethical approval (see Appendix 5).

2.6 Data Analysis

Correlations between the various measures (neuropsychological tests, questionnaires and demographics) formed the main analysis carried out in this study. Also, the MS group's performance on such measures was also compared to controls, as well as population norms where available. Both parametric and non-parametric analyses were run on the data obtained, having determined normality of distribution and equality of variance on results obtained for each individual measure. All statistical analyses were carried out using the Statistical Package for the Social Sciences for Windows (SPSS V.12). The size of the correlation coefficients are based upon the definitions provided by Cohen & Holiday (1982) shown in table 2.6 below

Table 2.6 Size of Correlation Coefficients

Coefficient	Description
.00 to .19	Very low
.20 to .39	Low
.40 to .69	Modest
.70 to .89	High
.90 to 1.00	Very high

2.7 Statistical Power

The most important assessment in the study was the SART; therefore power was deduced on this test. The numbers of participants used by Robertson *et al.* (1997), in his initial study using the SART with traumatic brain injured (tbi) patients, for two of the main hypotheses are given below:

- A significant difference (0.01 at 5% significance level) between a normal control group (n=17) and a tbi group (n=22) on SART performance was found with a total n=39.

- A significant correlation was found between tbi participants performance on the SART and the informant CFQ (0.44), but not with CFQ, using n=21.

The theoretical underpinnings of the present study's hypothesis suggest that a similar effect size would be expected within the MS population. Using the mean difference of 3.6 obtained in the aforementioned Robertson study, and common standard deviation of 4.233, it was found that a sample size of 23 in each group would provide 80 per cent power.

Assuming then a large effect size and taking alpha as 0.05, for comparisons Cohen (1992) states that power will be attained with a slightly more conservative sample size of 26 in each group. However, for correlation analysis Cohen states that a total number of 56 participants would be required, thus increasing the overall numbers required.

3 RESULTS

3.1 Participants

Fifty-seven individuals agreed to participate in this study: twenty-six people with multiple sclerosis forming the experimental group and thirty-one healthy volunteers forming the control group. For the purposes of clarity and succinctness the former group will be referred to from here on as the 'MS group' and the latter referred to as the 'control group'. All participants completed all the neuropsychological tests and questionnaires. All fifty-seven participants also elected a person who knew them well to complete a further questionnaire about them (informant CFQ). These were returned by fifty-three of the informants by the due date (1 control & 3 MS missing).

3.2 Normal Distribution & Equality of Variance

For each aspect of interest the data was satisfied for equality of variance using Levene's Test for Equality of Variance, and normal distribution by linearity of Q.Q. plots. The results of this indicated that it was appropriate to use parametric tests for the following aspects: age, years in education, estimated pre morbid IQ scores, SART error scores, SDMT scores, self CFQ, and anxiety ratings. The Levene value for each of these aspects is provided at the relevant sections. Unable to meet the assumption of equality of variance non-parametric tests were used for the following aspects: informant CFQ, depression, Elevator Counting, and Lottery.

3.3 Demographics of Participants

3.3.1 Gender

Table 3.3.1 below characterises the breakdown of participants with respect to gender and group. The percentages clearly show a balanced ratio of gender division across both groups.

Table 3.3.1: Gender Division across MS & Control Groups

	MS Group		Control Group	
	Count	%	Count	%
male	7	26.9%	8	25.8%
female	19	73.1%	23	74.2%

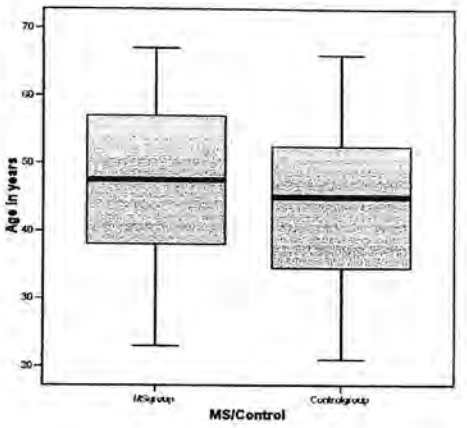
3.3.2 Age

The distribution of age of both MS and control groups are outlined in Table 3.3.2a below and visually represented in a boxblot in figure 3.3.2.

Table 3.3.2a Distribution of Age

Group	Minimum (years)	Maximum (years)	Mean	Std. Deviation
MS Group	23	67	47.62	12.274
Control Group	21	66	43.13	11.809

Figure 3.3.2



As table 3.3.2b shows, an independent samples t-test reveals a mean difference of 4.486 years of age, with the MS group being older. With a *p* value of .166 this difference is not found to be significant. The 95% confidence interval of (–1.921, 10.894) contains zero and therefore confirms that there is no significant difference between the two groups in relation to age.

Table 3.3.2b Age comparison between MS and Control Groups

		Levene's Test for Equality of Variances	t-test for Equality of Means					
		Sig.	Sig. (2-tailed)	t value	*df*	Mean Difference	95% Confidence Interval of the Difference	
							Lower	Upper
Age in years	Equal variances assumed	.798	.166	1.403	55	4.486	-1.921	10.894

3.3.3 Years in Education

The distribution of years in education of both MS and control groups are outlined in Table 3.3.3a below.

Table 3.3.3a Distribution of Education in Years

Group	Minimum (years)	Maximum (years)	Mean	Std. Deviation
MS Group	10	23	13.62	3.073
Control Group	11	22	15.26	3.245

The independent samples t-test, show in table 3.3.3b, demonstrates that there is a mean difference of 1.643 years in education, with the control group having had more. With a *p* value of .056 this difference is not found to be statistically significant.

Table 3.3.3b Comparison between MS and Control Groups on Years in Education

		Levene's Test for Equality of Variances	t-test for Equality of Means					
		Sig.	Sig. (2-tailed)	t value	*df*	Mean Difference	95% Confidence Interval of the Difference	
							Lower	Upper
Years in education	Equal variances assumed	.747	.056	-1.950	55	-1.643	-3.331	.046

3.3.4 Estimated Pre-morbid IQ

The estimate of pre-morbid IQ (i.e. IQ before the onset of MS for the MS group and current IQ in the control group) were obtained using the WTAR. The distribution of estimated IQ of both MS and control groups are outlined in Table 3.3.4a below.

Table 3.3.4a Distribution of estimated IQ

Group	Minimum (IQ)	Maximum (IQ)	Mean	Std. Deviation
MS Group	90	121	103.54	9.360
Control Group	91	121	108.16	7.510

An independent samples t-test goes shows that there is a mean difference of 4.623 in estimated IQ scores, with the control group having a higher IQ. With a *p* value of .043 this difference is found to be statistically significant, as shown in table 3.3.4b. Table 3.3.4c shows the distribution of estimated IQ on both groups when the clinical descriptions/ranges are used rather than IQ scores. This information will be used later in the discussion section when this aspect of the study is considered further.

Table 3.3.4b Comparison between MS and Control Groups on Estimated IQ

		Levene's Test for Equality of Variances	t-test for Equality of Means					
		Sig.	Sig. (2-tailed)	t value	*df*	Mean Difference	95% Confidence Interval of the Difference	
							Lower	Upper
Estimated IQ	Equal variances assumed	.076	.043	-2.069	55	-4.623	-9.101	-.145

Table 3.3.4c Distribution of estimated IQ using clinical description/ranges

	Totals	Estimated Pre-morbid IQ Range (counts)		
		Average (90-109)	High Average (110-119)	Superior (120-129)
MS Group	26	18	7	1
Control Group	31	19	10	2

3.3.5 Distribution of MS type and disease duration (MS group only)

The MS group contained 26 participants in total with MS type distributed as follows: relapse-remitting (n=4), secondary progressive (n=18), and primary progressive (4). The mean duration since diagnosis was 14 years, standard deviation 7, with minimum 4 years and maximum 30 years. The breakdown of MS type and its relationship to cognitive functioning was not however a focus of this study.

3.4 Order of Neuropsychological Test Presentation

As discussed in the introduction and methodology the order in which tests were given would be an important aspect of this study, since it would control for possible fatigue. Part of this aspect requires that the order of presentation does not significantly differ between the two groups. Table 3.4 shows that percentages of each of the six possible presentation orders across both groups are similar.

Table 3.4 Presentation order of Tests

Presentation order	MS Group		Control Group	
	Count	%	Count	%
A	5	20.0	5	15.6
B	4	16.0	6	18.8
C	4	16.0	5	15.6
D	4	16.0	5	15.6
E	4	16.0	5	15.6
F	4	16.0	6	18.8

Visually, this table suggests that the presentation order was evenly distributed between the groups. To confirm this, logistic regression was used since with only six possible fixed orders resulting in categorical data, a t-test could not be used. The number of people in each order of presentation, separately for each group (MS and control), was put into a logistic regression. A very good fit was found with a p value of .998 indicating that there was no difference between the groups in terms of the order of presentation. Evaluating the possible effect of presentation order will be provided later in this chapter.

3.5 Correlates

The nature and strength of relationships between the various factors involved in the study were analysed. These correlates are shown in table 3.5 below. The most relevant correlates with regard to the present study's aims have been extracted and summarised following the table.

Table 3.5 Performance Correlates of All Participants

		Anxiety score	Depression score	SART error	Mean SART RT	Elevator Counting	Lottery	SDMT	Self CFQ	Informant CFQ
Anxiety score	Pearson Correlation	1	.283*	-.101	-.098	.053	.152	.135	.356**	.100
	Sig. (2-tailed)	.	.033	.455	.469	.697	.260	.316	.007	.475
Depression score	Pearson Correlation	.283*	1	.179	.432**	-.370**)	-.330*	-.562**	.098	.406**
	Sig. (2-tailed)	.033	.	.182	.001	.005	.012	.000	.471	.003
SART error	Pearson Correlation	-.101	.179	1	-.196	.087	-.007	-.211	.058	.072
	Sig. (2-tailed)	.455	.182	.	.144	.521	.959	.116	.669	.608
SART RT	Pearson Correlation	-.098	.432**	-.196	1	-.319*	-.344**	-.367**	-.121	-.063
	Sig. (2-tailed)	.469	.001	.144	.	.015	.009	.005	.372	.652
Elevator Counting	Pearson Correlation	.053	-.370**	.087	-.319*	1	.455**	.506**	.147	-.552**
	Sig. (2-tailed)	.697	.005	.521	.015	.	.000	.000	.275	.000
Lottery	Pearson Correlation	.152	-.330*	-.007	-.344**	.455**	1	.562**	-.045	-.332*
	Sig. (2-tailed)	.260	.012	.959	.009	.000	.	.000	.740	.015
SDMT	Pearson Correlation	.135	-.562**	-.211	-.367**	.506**	.562**	1	.191	-.389**
	Sig. (2-tailed)	.316	.000	.116	.005	.000	.000	.	.154	.004
Self CFQ	Pearson Correlation	.356**	.098	.058	-.121	.147	-.045	.191	1	.184
	Sig. (2-tailed)	.007	.471	.669	.372	.275	.740	.154	.	.186
Informant CFQ	Pearson Correlation	.100	.406**	.072	-.063	-.552**	-.332*	-.389**	.184	1
	Sig. (2-tailed)	.475	.003	.608	.652	.000	.015	.004	.186	.

* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).

Summarising the correlations of attentional measures it was found that the SART (error score) did not correlate significantly with any of the other tests of attention (Elevator Counting, Lottery, SDMT), nor with everyday cognitive failures as measured by either self-reported or informant-reported Cognitive Failures Questionnaire, and not with measures of mood. Elevator Counting, Lottery, and the SDMT all significantly correlated moderately with each other at 0.01 level. These three tests also significantly correlated with mean SART reaction time.

The self-reported CFQ did not correlate significantly with any of the measures of attention. Thus, participant's opinion of their everyday cognitive failures was not able to predict how they performed on the attention tests, and vice versa, performance on

tests did not predict everyday functioning as perceived by the participants themselves. The informant-reported CFQ did significantly correlate with three of the attention measures; Elevator counting ($r = -.552$, $p < 0.01$), Lottery ($r = -.332$, $p < 0.05$), and SDMT ($r = -.389$, $p < 0.05$). The self-reported CFQ and informant-reported CFQ did not correlate with each other significantly ($r = .184$).

In terms of mood, anxiety and depression were significantly but lowly correlated ($r = .283$, $p < 0.05$). Anxiety did not correlate with any of the attentional tests. Depression however significantly correlated with Elevator Counting ($r = -.370$, $p < 0.01$), Lottery ($r = -.330$, $p < 0.05$), SDMT ($r = -5.62$, $p < 0.05$) and SART reaction time ($r = .432$, $p < 0.01$) but not the SART error score ($r = .179$). It is arguably important to note here that the mean depression score for each group lies within normal, non-clinical levels yet it still correlates with the aforementioned tests and will be discussed further latterly.

MS Group Correlations

The SDMT and Elevator Counting are significantly correlated with the informant-reported CFQ. The SDMT correlates with informant CFQ ($r = -.649$, $p < 0.01$) which is a higher than that of the correlations of all participants ($r = -.389$). Similarly the Elevator Counting correlates with informant CFQ ($r = -.621$, $p < 0.01$), slightly higher than that of all participants. In this group performance on the Lottery was not found to significantly correlate with informant CFQ ($r = -.341$), although the correlation was higher than that of all participants ($r = -.332$) which had been found to be significant at $p < 0.05$ level. Once again performance on the SART was not found to be significantly correlated with any of the other attention measures, nor with either of the

CFQ ratings, and not with mood. The SART reaction time was not found to significantly correlate with performance on the three other measures of attention, whereas it did when all participants were considered together.

Control Group Correlations

None of the tests of attention correlated with either the self-reported or informant-reported CFQ. Performance on the SART (i.e. SART error) did correlate with SART reaction time (r = -.455), indicating that the faster the reaction time the more mistakes were made in this group.

Table 3.5b below provides an overview of the correlations between the four attention tests with the two versions (informant and self-reported) of the CFQ, broken down into three groupings, all participants, the MS group alone, and the control group alone.

Table 3.5b Group Correlations of Attention tests with CFQs

Group	Informant-report CFQ correlations with...				Self-report CFQ correlations with...			
	SART error	Elevator Counting	Lottery	SDMT	SART error	Elevator Counting	Lottery	SDMT
All participants	.072	-.552**	-.332*	-.389**	.058	.147	-.045	.191
MS Group	-.106	-.621**	-.341	-.649**	-.098	.053	-.294	.006
Control Group	.242	NC	.002	-.054	.375*	NC	.051	.027

* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).
NC, cannot be computed because the Elevator Counting scores are constant.

The results suggest that the significance of correlations of informant-reported CFQs with attentional tests is weighted in the MS group rather than the control group. This was tested statistically using Fisher's *Z* (Clark-Carter, 1997). Fisher devised a way of transforming *r* into *r'*, which is normally distributed and allows the use of a *z*-test to

compare the correlations. Comparisons were carried out on the informant-reported CFQ with SART, Lottery & SDMT scores but not with elevator counting due to the constant value obtained in the control group. Table 3.5c demonstrates that only informant-reported CFQ correlated with SDMT showed any significant difference between groups (p=0.05), thus indicating that the significance obtained for all participants is significantly weighted by the results of the MS group. There was no difference found with the lottery but this may be explained by a lack of power in the analysis. Cohen (1992) states that the analysis required to compare correlations would require 66 participants in each group in order to reach power, numbers that this study did not aim to have. Given no significant correlations between SART performance and informant-reported CFQ's in either group it was expected that there would be no significant difference between the two correlations.

Table 3.5c Comparison of Correlations between Groups

Correlation	*Z* value	*P* value
Lottery/InformantCFQ	1.24	0.108
SDMT/InformantCFQ	2.56	0.005
SART/InformantCFQ	-0.50	0.309

3.6 Comparisons between MS and Control groups

3.6.1 Measures of Attention

Of the four tests of attention only SART (.995) and SDMT (.895) had sufficient equality of variance (value indicated in brackets) to use parametric tests of comparison. T-tests were carried out in order to compare variances within and between samples in order to estimate the significance between sets of means. The results provided in table 3.6.1a show that when comparing the MS group with the

control group there was no difference in the number of errors made on the SART, but there was a highly significant difference in performance on the SDMT.

Table 3.6.1a T-test Comparisons between groups on SART error & SDMT scores

	MS Group		Control Group		Levene	Mean Diff.	CI	*t* value	*df*	*P value*
	Mean	SD	Mean	SD						
SART error	11.00	5.146	9.03	4.673	.754	1.968	-.640, 4.576	1.152	55	.068
SDMT Score	32.31	11.00	57.81	12.952	.895	-25.499	-31.950, -19.048	-7.921	55	.000

Group comparisons on the Lottery and Elevator Counting tests were made using a Mann-Whitney test since the assumptions about underlying population parameters could not be made. On the Lottery test a *p*-value of < .001 was obtained (*U* value 203.00) thus indicating a highly significant difference between the two groups with the MS (median scaled score = 11) group performing worse than controls (median scaled score = 12) on this test of sustained attention. Comparing both groups mean scores with the normative data provides a clinical interpretation that supports this finding. The control group mean raw score (9.87) is equivalent to approximately the 50th percentile; the MS group mean raw score (8.076) is equivalent to approximately the 10th percentile.

Group comparisons on the Elevator Counting task were made using a Mann-Whitney test also. Once again a significant difference was found between the two groups with a *p*-value of < .001 (*U* value 263.50), with the MS group performing worse. The median score in both MS and Control groups was 7. Given the low ceiling effect on this test it was expected that a significant difference would be found due to the constant score of 7 in the control group (a value considered normal performance). Due

to the difficulty of the constant '7' score a one-sample t-test was carried out on the MS group alone in order to check if the means were significantly different from '7'. A *p* value of .002 was found (*t* value –3.434, *df* 25) thus supporting the finding that there is a statistically significant difference between the groups on this test of sustained attention. Whilst this result demonstrates a statistically significant difference, consideration of the clinical descriptions of the scores of the MS group, shown in Table 3.6.1b, will be made in the discussion chapter.

Table 3.6.1b Distribution of Elevator Counting Scores in MS Group

Elevator Counting Score	Interpretation	MS Group Nos. (n=26)
7	Normal	17
6	Doubtful	8
5	Definitely abnormal	1

Clinical interpretation of these results indicate that 17 of the MS group performed at the same level as the control group (normal level), 8 performed at level considered doubtful but not necessarily indicating impairment, and only 1 person performed at a level considered indicative of impaired sustained attention. This will be considered further in the discussion chapter.

3.6.2 Cognitive Failures Questionnaires

Analysis of the cognitive failures questionnaires involved three different aspects. Firstly, the self-reported CFQ scores were compared between the two groups using a t-test. The result, shown in table 3.6.2 below, demonstrates that there was no significant difference between the two groups on this aspect.

Table 3.6.2 T-test Comparison between groups on Self CFQ

	MS Group		Control Group		Levene	Mean Diff.	CI	*t* value	*df*	*P Value*
	Mean	SD	Mean	SD						
Self CFQ	36.08	14.268	42.32	10.616	.076	-6.246	-12.865, .374	-1.891	55	.064

The second aspect of analysis was to compare the informant-reported CFQ scores and this was done using a Mann-Whitney. The MS group obtained a median score of 38 (minimum 9, maximum 82) and the control group a median score of 33 (minimum 14, maximum 61). A *p*-value of .327 was found (*U* value 290.50) indicating that there was no significant difference between the two groups in terms of everyday cognitive failures as perceived by elected known persons of the participants.

The third aspect considered if there was a difference between self-reported CFQ and informant-reported CFQ within each of the groups, and this was achieved using paired sample t-tests. In the MS group there was no significant difference (*p* value = .238, *t* value –1.213, *df* 22) between self-report and informant-report of cognitive impairment as measured by the CFQ, although there was a mean difference of 5.87 with informants rating impairment higher than self-reports. In the Control group there was a significant difference (*p* value = .010) between ratings of impairment, with a mean difference of 7.267 with informants (known person) ratings less than self-reports.

3.6.3 Mood

Table 3.6.3 illustrates that the results of a t-test found that there was no significant difference between the groups on anxiety as measured by the Hospital Anxiety and Depression Scale.

Table 3.6.3 T-test Comparison between groups on Anxiety Scores

	MS Group		Control Group		Levene	Mean Diff.	CI	*t* value	*df*	*P* value
	Mean	SD	Mean	SD						
Anxiety	6.31	3.210	6.13	3.344	.985	1.79	-1.57, 1.929	0.205	55	.834

Comparison between the two groups on depression scores as measured by the HADS was achieved by means of a Mann-Whitney test. A p-value of $< .001$ was obtained (U value 101.00) thus indicating a highly significant difference between the two groups with the MS group (median 7) having higher depressive symptomatology than controls (median 2).

3.6.4 Fatigue

The parametric data that had been analysed was re-run this time adjusting for presentation order of the neuropsychological tests, thus providing an indication if fatigue had played a significant part in the scores achieved i.e. did the performance deteriorate with time. An Analysis of Covariance (ANCOVA) was used to achieve this. The results (see table 3.6A below) did not alter from previously reported, thus indicating that fatigue during testing was not a significant factor.

3.6.5 Taking Estimated Pre Morbid IQ into consideration

The parametric data that had been analysed was re-run once more, this time adjusting for the estimated pre morbid IQ scores that had been found to be significantly different between the groups at baseline testing. An Analysis of Covariance (ANCOVA) was again used to do this. All results (see table 3.6A below) were again similar thus indicating that estimated IQ was not a significant factor in the study.

3.6.6 Taking Depression into consideration

Once again the parametric data that had been analysed was re-run, this time adjusting for the depression ratings that had been found to be significantly different between groups at baseline testing. An Analysis of Covariance (ANCOVA) was again used to do this. All results (see table 3.6A below) were again similar thus indicating that depression was not a significant factor in the study.

Table 3.6A ANCOVA Comparisons between MS & Control Groups on SART & SDMT

		Results from original t-tests	Covariates		
			Presentation order (fatigue)	Estimated IQ	Depression
SART error	Mean Difference	1.968	1.952	1.364	1.418
	95% CI	-0.640, 4.576	-0.786, 4.950	-1.300, 4.028	-1.954, 4.789
	t value	1.152	1.483	1.026	0.843
	p value	0.68	0.144	0.309	0.403
SDMT	Mean Difference	-25.49	-25.799	-28.838	-21.75
	95% CI	-31.950, -19.048	-32.212, -19.396	-30.386, -17.290	-29.95, -13.55
	t value	-7.921	-8.065	-7.299	-5.318
	p value	0.00	0.00	0.00	0.00

3.7 Results in Relation to Specific Hypotheses

I. *The MS group will perform significantly poorer than the healthy control group across all the neuropsychological tests of attention carried out.*

Results

This hypothesis was upheld on three out of four of the neuropsychological tests of attention. There was a significant difference between the MS group and control group on performances on the SDMT (<.001), Elevator Counting (<.001) and Lottery (<.001) with the MS group performing worse. There was no significant difference between the same two groups SART performance (.068).

II. *There will be a significant difference between the MS group and the healthy control group on the informant-reported Cognitive Failures Questionnaire.*

Results

A *p* value of .327 using a Mann-Whitney test indicates that there was no significant difference between the two groups in terms of everyday cognitive impairment as perceived by elected known persons of the participants. Thus the hypothesis was not upheld.

III. *There will be a significant difference between self-reported and informant-reported CFQ scores in the MS group.*

Results

Using a paired samples t-test an obtained *p* value of .238 demonstrates that within the MS group there was no difference between the ratings of participants and informants on the cognitive impairment of the participants. This hypothesis was therefore not upheld.

IV. *Performance on the Sustained Attention to Response Task (SART) will significantly correlate with everyday cognitive failures, as measured by the informant-reported Cognitive Failures Questionnaire (informant CFQ).*

Results

This hypothesis was not upheld since performance was not found to significantly correlate with the informant-reported CFQ.

V. *The SART will correlate with the informant CFQ more strongly than the other attentional tests (Lottery, Elevator Counting, and SART), and hence be a stronger predictor of everyday cognitive functioning.*

Results

The Lottery, Elevator Counting and SDMT all significantly correlated with the informant-reported CFQ, whereas the SART did not. Thus the hypothesis was not upheld.

VI. *Performance on the SART will correlate with other measures of sustained attention*

Results

The SART did not correlate significantly with any of the other measures of sustained attention i.e. Elevator Counting and Lottery. Thus, the hypothesis was not upheld.

4 DISCUSSION

In this discussion section each of the five specific hypotheses tested will be delineated and the relevant results expounded upon. Due to the relationship between the hypotheses there will inevitably be some overlap in discerning the important aspects of each. The implications for future research as well as clinical implications will be drawn upon. Issues of a methodological and ethical nature will also be discussed.

4.1 Hypotheses

4.1.1 Hypothesis I: The MS group will perform significantly poorer than the healthy control group across all the neuropsychological tests of attention carried out.

It was acknowledged in the introduction that there is considerable debate surrounding the prevalence and nature of attentional impairment in MS. Some authors have found that no impairment exists at all, others that it is only mild impaired and then only in a few cases, and yet others have held that it is one of the most prominent symptoms of MS. In particular it had been identified that MS patients may be more susceptible to impairments of sustained attention. Given the heterogeneous nature of MS primarily based on the variability of lesion location and severity, it was out with this scope of this study to presume to provide an answer to the nature and prevalence of attentional impairment in MS. However, the study was based on the fundamental assumption that the MS population on the whole are more likely to develop attentional problems. The

first hypothesis therefore set out to show that there was a difference between MS and control samples in this study on four tests of attention.

The results indicated that indeed there was a significant difference in attentional ability between the MS group and controls, on three out of four of the tests. Thus in a group of MS patients regarded by medical staff to be cognitively impaired, attentional impairment is found to be part of the cognitive profile. In order to establish what these results mean it is important to look at each of the four tests disparately.

Sustained Attention to Response Task (SART)

The nature of the SART was one of the principal reasons behind the development of the present study. Studies using traumatic brain-injured patients had shown the SART, in part, to be a sensitive measure of mild impairment of sustained attention. It was therefore deemed to be potentially useful for using with MS patients, where it had been suggested that such impairments might be mild.

Despite this, results on the SART revealed no significant difference between the two groups. The obvious implication that no difference exists between the two on sustained attention ability however arguably cannot be drawn. The fact that there is a significant difference between the two groups on the other two tests of sustained attention, Lottery and Elevator Counting, suggest that an alternative explanation is required. The SART scores were unable to distinguish controls from MS, even though these differences were found in other tests.

The mean SART error in the control group was 9.03 and 11.00 in the MS group. In the original SART study (Robertson *et al.*, 1997) the mean SART error in the control group was 4.0 and 7.6 in the brain-injured group. A second possible explanation then for the results of the present study is that the control group performed very poorly. If one compares the MS group with the results of the original study then it would seem clear that there are deficits in the group, when compared to controls and indeed brain-injured. However, if this was the case one would have expected the controls to perform similarly poorly on the other tests of attention also, which they did not thus suggesting an alternative explanation is required.

These results do however give rise to the question of validity in the original study. There is considerably disparity in performance between controls in the two studies despite administration being precisely the same. Looking at the available demographics does not reveal any huge differences, although the mean age is 7 years older in the present study but this is arguably not suffice to proffer an explanation for the difference. Time spent working on the SART as well as observations made during testing leads the researcher to the opinion that it would be very hard to achieve a mean of 4.0. Only 4 of 31 of the present study's controls obtained 4 or less errors. It is certainly an area that requires investigation if the SART is to continue to be developed for use with any population.

Despite this the findings that the MS group did not significantly differ from controls in the present study were a surprise to the researcher given observations made during testing which indicated that as a group they struggled with this test. It was therefore decided to briefly re-examine the overall performance of participants on the SART.

The SART error is calculated from the number of times that an individual presses the button when a '3' is presented on the screen. Because the individual habituates to pressing the button for the other numbers it requires sustained attention to inhibit pressing when a three is pressed. However, the test does not build in for the alternative error of not pressing the button when a person ought to i.e. on presentation of numbers 1, 2, 4-9. Examining the data reveals that the MS group failed to consistently do this and hence may explain why they were able to not press on the '3s' when required i.e. they did not fully habituate to pressing the button. This may provide a third possible explanation for the results obtained.

Speculatively exploring this notion little further, an error point was given for every incorrect non-press and added to the original error score, thus providing an overall error score, and then comparisons made. The results of a t-test demonstrate a significant difference (p value 0.01) between the MS group (mean overall error 37.12) and the control group (mean overall error 13.84). Based on observation, this occurred because after unintentionally pressing on a '3' the MS patients took longer to focus attention back on the task. When the overall error is considered in correlation analysis it is found that it significantly correlates with Elevator Counting ($r = -.389$, $p < 0.01$), Lottery ($r = -4.00$, $p < 0.01$), SDMT ($r = -.595$, $p < 0.01$), informant CFQ ($r = .532$, $p < 0.01$), and with depression ($r = .278$, $p < 0.05$). These results can only be regarded speculatively but serve here to highlight a third possible explanation as to why the SART was not able to differentiate between the two groups. Further research would be required to demonstrate why MS participants performed this way, however, one possible interpretation is that they displayed impaired of sustained attention on the SART since they were distracted from task, but that the scoring system did not enable

recording of this. Three other possible explanations for the pattern of results obtained on the SART are discussed in more detail in section 4.2 (page 111). These are the suggestions that the SART is simply too hard for MS participants due to the visual and motor components, that poor information processing speed affected the MS participant's ability to habituate, and finally that the SART is not a reliable test.

Elevator Counting & Lottery

These two tests of sustained attention, part of the Test of Everyday Attention, have a low ceiling effect and hence are only useful for differentiating people with quite obvious attentional problems. Indeed, Higginson *et al.* (2000) considered them unsuitable in their study because they believed that MS patients would manage them easily. However, the results on both tests showed a significant difference between the MS group and the control group. On these tests the hypothesis was upheld and demonstrates that sustained attention deficits are part of the profile of cognitive impairment in MS.

Clinical interpretation of these results suggests that the Lottery test is a more sensitive test of impairment in MS than Elevator Counting. Comparing the mean raw score of the control group with the test normative data demonstrates that the performance was equivalent to approximately the 50^{th} percentile, which is what one might expect. The MS group's mean raw score was found to be equivalent to approximately the 10^{th} percentile thus indicating impairment.

In the Elevator Counting test clinical interpretation of the results suggest that it is not a sensitive test of mild impairment and therefore not suited to MS. All control group

participants score a maximum seven points, indicating a normal performance. 17 of the MS group scored seven points also, indicating a normal performance. Eight of the MS group scored six points which is considered to be 'doubtful' and only one person scored '5', considered to be definitely impaired. This test would not be useful as a screening measure since it appears that many people with MS may do well on it, despite having attentional impairment as measured on the Lottery or the SDMT.

Symbol Digits Modalities Test (SDMT)

Results on this test demonstrated a significant difference between the two groups, thus replicating previous results and proving why it is the current recommended test of attention in MS. The debate about whether it is purely a test of information processing speed or whether it has an attentional loading remains and will be considered further on in the discussion.

Overall, on the three established and published measures of attention the hypothesis that there would be a difference between the MS group and controls was upheld.

4.1.2 There will be a significant difference between the MS group and the healthy control group on the informant-reported Cognitive Failures Questionnaire.

Self-report measures of cognitive problems can be of use in examining cognitive problems not easily addressed by neuropsychological tests, such as attention, and they can also be useful in highlighting areas of daily living that are disrupted by cognitive

deficits. One advantage of self-report measures of cognitive function is that they consider the environmental context in which cognitive problems are expressed (Sullivan *et al.*, 1990).

Concerns have been raised about the validity of such measures based on the assertion that people with cognitive problems may not have insight into the severity of their difficulties. Also, the nature of cognitive impairment may not enable awareness of difficulties. For example, an individual with memory problems may forget experiences cognitive difficulties thus rendering them unable to accurately assess it. Emotional status and individual coping style may also affect the reliability of such measures; for example, some people may remain in denial about their difficulties.

However, it could also be argued that healthy individuals might also be susceptible to inaccurate assessment of their own levels of cognitive functioning. One reason may be that having greater awareness of their internal mental state and subtle aspects of behaviour people are likely to be more acutely aware of everyday cognitive functioning than an informant who observes periodically overt incidents of cognitive difficulties.

Due to the potential bias of self-report measures it seemed reasonable to suggest that the views of informants would more accurately report the everyday cognitive functioning of participants. The second hypothesis therefore asserted that there would be a significant difference between the two groups cognitive functioning as measured by the informant-reported CFQ. Results indicated that there was no difference between the two groups and the hypothesis was therefore not upheld.

There was however a significant correlation between three of the attentional tests and the informant CFQ, with poor scores of ability on the tests matching informants ratings of cognitive difficulties. This relationship indicates that the informant CFQ is recording roughly what might be expected in terms of neuropsychological testing. However, because the informant CFQ ratings were unable to differentiate between the two groups that had through neuropsychological testing been shown to be different in terms of attention impairment, it suggests that the CFQ may lack sensitivity and should not be used in isolation when assessing or quantifying cognitive impairment.

There was an interesting dynamic in the relationships of reported CFQs which requires comment with regard to this second hypothesis. In the control group the self-reported CFQs were higher than the informant-reported CFQs, yet the direction of difference was opposite that in the MS group with self-reported CFQs being lower than informant-reported CFQs. If the relationship between self and informant ratings in the control group is assumed to be representative of normal performance ratings then a true comparison with the MS group should arguably examine if this relationship exists too in the self and informant ratings of the MS group. The relationship between self and informant reported CFQs is not mirrored in both groups suggesting that there is a difference between the two groups. This suggests that whilst the second hypothesis could not be upheld in terms of statistical difference between ratings, used qualitatively in clinical practice in may serve to indicate that there is need for further investigation.

4.1.3 There will be a significant difference between self-reported and informant-reported CFQ scores in the MS group.

The third hypothesis stated there would be a significant difference between self-reported and informant-reported CFQ scores in the MS group. Whilst the CFQ is not a test of insight *per* se Robertson *et al.* (1997) asserted that in the traumatic brain-injured population differences between the self and informant ratings on the CFQ may be due to a lack of insight of cognitive difficulties on the patient's part. The researcher in this present study assumed 'lack of insight' to be have been used in its broadest sense and includes: a specific organic impairment of insight, lack of awareness secondary to cognitive impairment e.g. forgetting one forget, and psychological reactions e.g. denial. The results showed that there was no significant difference between the self-reported and informant-reported ratings of everyday cognitive difficulties in this MS sample. One therefore could not infer from the CFQ scores that the MS patients 'lacked insight' into their difficulties.

One of the difficulties with such a measure as the CFQ is that there are no norms provided. However, the original introduction to the CFQ (Broadbent *et al.*, 1982) provides figures on a sample of male, neurologically intact participants. This group provided a mean rating of 43.32 and therefore provides a point of comparison in relation to results obtained by the control group in the current study. The current control group self-reported CFQ mean was 42.32 which very closely meets the Broadbent *et al.* figure.

In the present study the MS group's mean self CFQ rating was 36.08 which turned out not to be significantly different from the self CFQ ratings of controls (42.32) but nevertheless is lower than what would be expected. It has been demonstrated through the neuropsychological tests that this group have attentional impairment hence it would arguably be expected that their ratings cognitive functioning would be higher than controls. The fact that the self CFQ ratings of the MS group are not higher than the controls suggests that the MS group lacked awareness of their difficulties.

4.1.4 Performance on the Sustained Attention to Response Task (SART) will significantly correlate with everyday cognitive failures, as measured by the informant-reported Cognitive Failures Questionnaire (informant CFQ).

One of the main features of the SART, which has fuelled considerable interest in the test, is the claim by authors that it is the first laboratory test on which performance predicts attentional slips in everyday life. As highlighted in the introduction the ecological validity of tests is becoming an understandably important area within neuropsychology. It is arguably not sufficient to be able to say only that there is impairment from a previous level of ability; people wish to know what it will mean in their everyday lives, thus tests that are predictive.

The results demonstrate that this feature of SART was unable to be replicated in the present study using MS patients. Performance on the SART by all participants did not correlate with informant-reported CFQ. However, section 4.1 of this discussion

chapter has alluded to a potential problem of scoring with the MS patients on the SART. Once again a speculative examination of overall errors on the SART (i.e. not pressing when participants should have) found that this did correlate significantly ($r = .532$, $p < 0.01$) with informant CFQ. This may suggest that if the problem with the scoring system was resolved then the results may have been positive and the hypothesis upheld.

The finding that performance on the SART does not correlate with CFQ cannot be fully explained however by the potential scoring problem in those with MS. The original SART study found that the performance of controls significantly correlated with self-reported CFQ ($r = -.27$, $p < .05$) and also with informant-reported CFQ ($r = -.29$, $p < .05$). The correlations may be considered low but nevertheless they were both significant. In the present study the performance of the control group did not correlate significantly with either the self or informant-reported CFQ. On top of the mean scores of the controls this result gives rise to serious differences between the present and initial SART study. If the results had demonstrated that it was not a test suitable for MS then that would have been a worthwhile investigation on its own, but these differences suggest that there is a need to examine more thoroughly the initial findings on the SART.

4.1.5 The SART will correlate with the informant CFQ more strongly than the other attentional tests (Lottery, Elevator Counting, and SART), and hence be a stronger predictor of everyday cognitive functioning.

Robertson *et al.* (1997) found that the SART correlated more strongly with the informant-reported CFQ than another test of attention (Triplets test) and they proposed that this was due to the additional sensitivity of the SART to mild attentional deficits in traumatic brain-injured patients. The literature review acknowledged that MS patients tend to score normally on most screening measures of general IQ which often include an attentional component. One explanatory theory is that impairments of attention in MS are likely to be mild if present at all. Thus in the present study hypothesis five held that the SART would correlate more strongly than the other tests of attention, due to its sensitivity to mild attentional impairments.

As reported in 4.1.4 the SART did not correlate at all with the informant-reported CFQ. The Lottery, Elevator Counting and SDMT however all significantly correlated with the informant-reported CFQ. Thus the hypothesis was not upheld. On this sample of MS patients the SART was not found to be a sensitive measure of sustained attention.

Performances on the other three tests were however associated with everyday cognitive failures as perceived by people known to the participants. Contrastingly, self-perceptions by participants were not significantly correlated and hence not associated with test performance. Relating back to the previous discussion regarding insight into cognitive difficulties these findings suggest that it is important to consider

the reports of informants who know the patient well and not simply to rely on self-reports.

4.1.6 Performance on the SART will correlate with other measures of sustained attention

The SART was developed in part due to the recognition that currently available neuropsychological tests of attention were firstly not sufficient to adequately characterise attentional deficits, and secondly were not up to date with current theoretical opinion of anatomical subdivisions of attention. The various sources of literature referred to in the introduction shared a common opinion that as the ability to assess attention improves, its role in mediating recovery becomes more apparent. Without wishing to regurgitate the introduction, it has become clear that future tests of attention would be required to delineate which different types of attention they were measuring.

The authors of the SART assert that it is to a great extent a measure of sustained attention. This would imply that performance on it would obtain a stronger relationship with other tests of sustained attention than other attentional tasks, and in particular with tests where response inhibition is important. This formed one of the hypotheses for this study which on the basis of the author's assertions stated that performance on the SART would correlate with other measures of sustained attention i.e. Elevator Counting and Lottery. The results demonstrated no significant correlation

between the SART and these two tests; nor did it correlate with the other measure of attention, SDMT.

Even if the aforementioned suggestion that the scoring system is problematic could be demonstrated as valid it certainly could not fully explain why performance on the SART did not correlate with the other attentional tests. One would have expected the correlations to exist in the performances of the controls, which it did not. Within the control group the SART did not correlate with either the Lottery or the SDMT, and was not computable in the Elevator Counting due the constant scoring on that test. This represents yet another significant difference from the original SART study (Robertson *et al.,* 1997) and brings into question the validity of the SART as a whole.

4.2 General comment on all the findings

The principal assessment tool in this study was the SART. Research on traumatic brain injured patients suggested that the SART was an assessment tool sensitive to mild sustained attentional impairment, it was predictive of everyday cognitive difficulties, and also had the potential to help with rehabilitation of attention. The test is also grounded in current theoretical opinion asserting several independent attention systems. Such potential necessarily called out for testing in the MS population, where the literature on attention impairment has suffered, in part, from inadequate tests.

The results on this first study using SART with MS patients have not replicated the positive findings in other populations. All hypotheses involving the SART were not upheld. There are several plausible explanations.

One possible explanation for this has already been expounded upon in this discussion chapter and suggests that the scoring system fails to pick up alternative errors. Observations during testing and an examination of the raw scores indicated that when MS patients pressed on a '3' unintentionally they subsequently took several more stimuli presentations before regaining focus on the task. This pattern occurred with only a few of the controls. It arguably suggests that sustained attention problems were evident but that the scoring system did not pick it up. However, an alternative to this would need to be proved through specifically designed research since there are alternative interpretations.

Another credible interpretation of the results is that the SART was simply too hard for the MS patients to do. Initial reservations existed during the design of the study because of the visual and motor components. Although the SART does not place heavy demands on fine visual acuity or on motor co-ordination, it was recognised that if this test was going to be developed for future use in MS then these aspects of the test would need to be reviewed. For the purposes of discovering whether the SART held any potential for this population, people were screened for visual and motor insufficient to do the task. It is possible however that the sustained length of the test took its toll on these functions even in those deemed as proficient.

Perhaps one of the most plausible explanations for the results obtained in the MS group lies in their information processing speed ability. The test stimulus requires the participant to respond at a rate of just over once per second. The results of the SDMT suggest that the MS group as a whole had impaired information-processing speed, which suggests that they may have difficulty on relatively quick response tasks like the SART. Once again observations made during testing and examination of the raw scores do not suggest that this is what was happening since many of the MS group were able to respond appropriately for several stimuli presentations in a row. If information processing was problematic then one may arguably expect a more broken up pattern of response. This is further supported from examination of the reaction times. Whilst there was a significant difference between the two groups in terms of reaction time on the SART, which was expected, the mean reaction time of the MS group was 402 milliseconds (76 ms slower than controls) and well within the 1150 milliseconds period each stimulus presented.

These possible explanations to the results of the MS group required to be researched specifically before firm conclusions can be drawn. However, perhaps the negative findings on the SART in this study highlight a more serious problem that is unrelated to the population it was used on. To gain poor results with the MS population may have been possible and even arguably predictable, in which case it could have been concluded that it is simply a test not suitable for use with this population. However, if the SART is all the authors claim then one would expect the results of the control group to reveal a similarity with those in the initial SART study: they do not.

In the initial study the controls obtained a mean SART error score of 4.00, it correlated both with the self CFQ and informant CFQ, and correlated with the Lottery test. In the present study the mean SART error score for controls was 9.03 which is not only a lot higher than the initial study's controls but worse than the traumatic brain injured patients. As previously noted only four of the present study's controls got four or less, thus suggesting that the difference between the two studies findings is great. The SART performance of controls did not correlate with informant CFQ, nor did it correlate with another test of sustained attention (Lottery test). It did however correlate with self-CFQ. The difference in the performance of controls between these two studies was considered to be so great that a review of the set up of the SART was once again compared to confirm that they were the same in each study. The SART is a new laboratory paradigm and perhaps the only conclusion that can be reached with regard to it here is that there is a need for much more research to be carried out on it in determining its validity and reliability.

Despite the problems with the SART, results obtained on the other neuropsychological tests of attention revealed some important findings. Fischer *et al.* (1994) concluded that the degree to which cognitive dysfunction in MS impacts on everyday functioning remains unknown. The TEA is a battery of tests which distinguish between different types of attention and also aims to be ecologically valid, thus more predictive of functional ability. Quite surprisingly the TEA had only been involved in one study with MS, and within that study the subtests of Lottery and Elevator Counting were omitted due to expected low ceiling effects, implying that there was insufficient variability to measure mild impairments in MS. Indeed, the present study did discover this low ceiling effect, yet despite that, a significant

difference between the MS and control groups was found. Whilst the present study would concur that these subtests of the TEA do lack variability and sensitivity to pick up mild impairment, the significant difference found demonstrates that sustained attention impairment is a significant part of the cognitive profile of MS patients. The Lottery and Elevator Counting tests may therefore be considered potentially useful in the clinical neuropsychological assessment of MS patients.

A review of the literature revealed a classic neuropsychological difficulty existed within the assessment of attention in MS, the differentiation of information processing speed from attentional functioning. This is because the latter is necessary for performing any speeded cognitive task. For example, if an individual is not responding appositely within a social conversation it may be because they are unable to sustain their attention on the task. It may also be that their ability to focus their attention on the conversation whilst in a room where there is a lot of distraction is impaired. However, it may be also be that the conversation is simply too fast for them to take on the information and respond appropriately at the correct moment.

The literature review recognised that it has been consistently found that MS patients exhibit deficits on the oral version of the SDMT. This it seems is usually interpreted to slow information processing but van Zomerer and Brouwer (1994) point out that the SDMT is often considered to be a measure of attention within clinical and research work. As expected the MS group did perform poorly on the SDMT relative to controls. Results also demonstrated that the SDMT correlated with Lottery and Elevator Counting, both of which do not have a heavy speed of information processing component. This may suggest that the SDMT does have an attentional

component as well as that of information speed processing, but further research would be required to demonstrate this. At the very least the results demonstrate that the SDMT is not sufficient in itself to adequately assess attention since clearly there are problems of sustained attention within MS that are unrelated to information processing speed, and thus require to be a part of assessment.

4.3 Implications for future research

There are five main implications for further research drawn from the findings of this study.

The first concerns the principal assessment tool of the study, the SART. The results of the control group in this study differed significantly from that of the original SART study (Robertson *et al.*, 1997) arguably indicating that the validity and reliability of the SART still requires to be established in healthy controls before being tested on clinical populations.

The second issue concerns the scoring of the SART. The test assumes impaired sustained attention to be demonstrable by failure to inhibit pressing the button when presented with a '3'. The present study found that MS patients were able to do this as well as controls. However, it was observed that in general their response to having unintentionally pressed on a '3' was to lose focus and subsequently miss the next few presses. It may be that the MS group was unable to fully engage in the SART due to variety of reasons already outlined in this discussion section. Another possibility was

that the pattern of their performance demonstrated impaired sustained attention ability but that the scoring system did not account for it. It is also noted that several of the controls did likewise but were able to get back on track much sooner. None of the other studies using the SART refer to similar observations though it seems likely that it would have been present. This aspect highlights that the whole pattern of response rather than just the error score on SART performance needs to be examined through research in order to establish why such a pattern of response occurs and how it might be understood.

If the first two aspects alluded to could be resolved then a third issue would concern repeating the present study. If the SART is going to prove itself a useful test within MS then the results gained in this study suggest that it would be advisable to have a third group. The addition of an MS group who were matched on physical disability with the experimental MS group but who were not cognitively impaired would help to demonstrate if any poor performance found was due to cognitive and not visual or motor impairment.

The fourth issue regards the finding of specific sustained attention deficits in the MS group. In an area where clarity is lacking, this first study to use the Lottery and Elevator Counting subtests of the TEA demonstrated that sustained attention impairment is a part of the cognitive profile for some people with MS. Given that these tests are not thought to be very sensitive to mild impairment this leads to the notion that appropriate tests of sustained attention sensitive to mild impairment are still required. Many tests are initially developed for use with other populations and

hence a broader research requirement would be the development or adaptation of tests appropriate for MS.

The final and arguably most important implication for research advancing from this study is that in identifying sustained attention impairment in MS it suggests that the theoretical subdivisions of attention require to be investigated further. A future avenue of research would therefore be to discover more about the range and severity of distinct types of attention deficits, and in essence more accurately characterise the nature of potential attentional impairment in MS.

4.4 Implications for clinical practice

There are five main implications for clinical practice drawn from the findings of this study.

The first implication is that the results demonstrate that the CFQ is not sensitive enough to assess for cognitive impairment, thus should not be used in isolation but in conjunction with psychometrics, observation and interview. This simply falls in line with good clinical practice. The results also show that the informant-reported CFQ is important since it correlated with the neuropsychological tests and therefore are more accurate than the self-reported CFQ. Obviously the closer the self-report is to matching the informant-report when a person is cognitively impaired then the more indicative this may be of insight ability. If they two reports are not similar then one cannot conclude that there are insight issues, however, it should indicate then need for

further clinical assessment. Such information could help to open up discussion on what the underlying issue is.

The second issue concerns patient insight into cognitive impairment. The study was unable to demonstrate through the use of self and informant reported CFQs that the MS group lacked insight. The lack of sensitivity of the CFQ, as well as the psychological influence on ratings, suggests that the use of the CFQ may not be a particularly useful way of assessing insight or awareness of difficulties.

Whilst not considered a measured of sustained attention that is sensitive to mild impairment the Lottery test may nevertheless serve as a useful assessment for using with MS patients. It was able to discriminate that some MS participants had sustained attention deficits and in the absence of other sensitive and valid tests, can provide some measure of ability. The Elevator Counting was the least sensitive test and whilst it did find a difference between the two groups, clinically it lacks sufficient variability and sensitivity to monitor continued cognitive decline, sufficient only to acknowledge obvious and definite impairment.

The fourth clinical implication has now been made clear several times throughout the discussion section. The SART should not be considered for using with MS patients, even ones that have no visual or motor difficulties, since it has been found in its current form to lack validity and sensitivity.

The final implication drawn from the results is that the SDMT was found to a sensitive measure of impairment that was predictive of everyday cognitive

functioning, thus consistent with previous research findings. However it was also argued that in correlating with two of the sustained attention tests it was no longer sufficient to interpret poor SDMT performance as down only to information processing speed deficits. The residual implication is that whilst the SDMT is a useful measure of attention, clinician's need to use it in conjunction with other tests of attention to characterise impairment fully.

4.5 Critique of Methodology

There are a number of methodological issues with regard to this present study that will now be discerned and delineated.

4.5.1 Selection of Experimental Group

Due to the heterogeneous nature of MS (e.g. variability in symptoms, type, duration etc) an important methodological issue arises with regard to patient diagnosis and selection. The provision for guidelines for neuropsychological research in MS by Peyser *et al.* (1990) suggests that patients not meeting the criteria for definite MS should be excluded from study, and this was adhered to here.

Many studies of MS have selected experimental groups on the basis of physical disability, disease duration, or disease type. The literature review indicated that such variables have been shown not to link with the nature and course of cognitive

difficulties. Selection based on these variables it is argued can only be useful when evaluating the relationship between such variables and cognitive impairment but is not sensible in studying the underlying mechanisms of cognitive decline. Kujala *et al.* (1995) state that subdivision according to cognitive status is a better method for studying cognitive impairment. This approach was adopted in the present study and the experimental group selected on the basis of being deemed cognitively impaired by medical staff.

The study may have benefited from carrying out a screening of overall cognition and on the basis of this determine if potential participants were cognitively impaired or not. This was considered but for several reasons declined in favour of clinical interpretation. The researcher had previously carried out a screening assessment (Repeatable Battery for the Assessment of Neuropsychological Status; Randolph, 1998) with an MS patient within clinical work and hence estimated that it would have required a further two sessions of one-hour duration with each potential participant to complete this. It was felt that this would be asking too much of the participants who would be receiving nothing in return, it was significantly outweighing the time for the actual area of interest, and it would not provide much information since MS patients tend to do well on such general measures. To carry out screening measures would have added considerably to the limited time in which the study was to be carried out in, making it difficult to complete.

Increasingly researchers are selecting community-based populations of people with MS. Results from these studies are more representative of the total population of people with MS, and hence more generalizable than those from obtained from

samples gathered via hospitals and out-patient clinics (Brassington & Marsh, 1998). Whilst several of the participants were community based the design of the study was mainly based on hospital and out patient attendees. Although the study was not aiming to examine prevalence rates for which a community sample is required, it is acknowledged that the study if developed in the future would be enhanced and more useful if it employed a community-based sample.

4.5.2 Selection of Control Group

The principal assessment tool in this study, the SART, is only newly developed and as yet does not have established validity and reliability. It was essential therefore to have a control group for comparisons of performance. The use of a control group can often be a pivotal element of careful experimental design and most studies use healthy participants to form this group, as did this study. The two groups were matched as far as possible on age, gender, estimated premorbid IQ and years in education, in line with many other studies in the area.

The negative findings of the SART were hard to interpret and thus the study may have benefited from having the healthy control group and also an MS group with no cognitive impairments but matched in physical disability. This may have helped to support the notion that sustained attention impairment contributed to the performance observed by more effectively controlling for motor and perceptual factors.

4.5.3 Test Selection

The justification for test selection has already been provided and since the study centres on the SART sufficient time has already been given to it throughout the discussion chapter and need not be reiterated. It was conceived that the application of the SART might only be appropriate for a select group of MS patients due to the fact that it does require a minimal degree of motor and visual ability that not all MS patients may have. Thus it was recognised at the outset that any positive results obtained would not lend itself to a generalisation of the appropriateness of the SART for all MS patients. Nevertheless, it was believed that if the positive assets of the SART shown in the traumatic brain population could be replicated in a select group of MS patients, then there would be justification for further development of it and an attempt to make it valid for more MS patients. Despite this acknowledgement, the researcher is keen to point out that the visual and motor demands of the SART are minimal, and arguably compare with other tests. For example, the visual acuity required is much less than that for the currently recommended SDMT.

4.5.4 Consideration of Affect

It was apparent from the MS literature that patients can experience high levels of mood disturbance. Despite the recognition generally that affect can influence cognitive functioning, especially attention (Lezak, 1995), no studies have established a correlation in MS. This may be due to the fact that the effect of mood on cognition in MS has not been widely considered. Hutchinson *et al.* (1996) state that depression

in particular ought to be taken into consideration in subsequent analysis of data pertaining to cognition.

Mood was taken into account in this study. Whilst a significant difference was found between the MS and control groups on depression both were well in the 'normal' range as measured by the HADS, thus not included as a confounding variable in other analysis. It may be considered that both groups scored lower than one might expect. The HADS was selected on the basis of recommendation within the literature, since is circumvents physical symptoms that might bias scores. Whilst this was satisfactory for the present study, the literature did reveal this area of MS to be very under-researched and requires considerable focus in future studies.

4.5.5 Ethical Issues

Section 2.5 outlines the ethical considerations for the present study. Completion of the study gives rise to comment on two of these issues. It was considered that participation in this study would not cause distress to anyone and this proved to be the case. Several people reported finding the Lottery test extremely dull and frustrating because whilst they knew it was going to last a long time (10 minutes) during the test they were not aware of how much time had passed.

Everyone was made aware before consenting to participate that they would not receive feedback on their own individual results; rather, they would be sent a summary report of the general findings. The participants who consented one assumes

felt okay about this. However, for the researcher it proved to be a challenge and a frustration. Many of the MS participants were seen in their own homes and many wanted to share their story, often of frustration with services and in particular the feeling of not being listened to. For some of these people it was clear that cognitive and psychological problems (e.g. affective disturbance, relationship difficulties) were contributing to their difficulties yet they were not receiving psychological input from services. Recognising need but not being able to do anything about it, particularly when participants were giving of their time, was a personal challenge.

4.6 Conclusions

In reviewing the literature it was recognised that despite significant advances having been made in the area of cognitive functioning in MS there is a tremendous need for more research into many aspects of it. In a review of the neuropsychologcal aspects of MS Brassington & Marsh (1998) identified the need for more information on the range and severity of cognitive deficits, to evaluate the effect of cognitive disturbance on the patient's everyday functioning, and need for the development of appropriate tests.

Based on a current theoretical model of attention this study focused on the specific area of sustained attention and purported to examine the use of three recently developed neuropsychological tests of sustained attention. In doing so the study demonstrated that in this sample of cognitively impaired MS participants, sustained attention is part of that profile of cognitive deficits. The principal assessment tool was

the Sustained Attention to Response Task (SART) but in its current format was not found not to be a valid measure for using with the MS population. Having recognised that sustained attention is an aspect for consideration with this population then the research need identified by Brassington & Marsh still applies.

The desire to understand, to find solutions, to develop improved ways of disease management and to contribute through research to all of these aims was overwhelmingly evident in the MS participants and their families. It is of interest to note that despite the impairment found, of the experimental group (twenty-six participants with MS recognised as having cognitive impairment) only seven participants had ever been assessed by a psychologist and that occurred as common practice during hospital admissions not as a result of referral. At the very least it is hoped that the process and findings of this study has highlighted the need for identifying and assessing thoroughly the cognitive functioning in people with MS. From the researchers perspective it has provided the stimulus, foundation and motivation for further research into attentional impairment within multiple sclerosis.

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APPENDICES

Appendix 1

The Pathology of Multiple Sclerosis

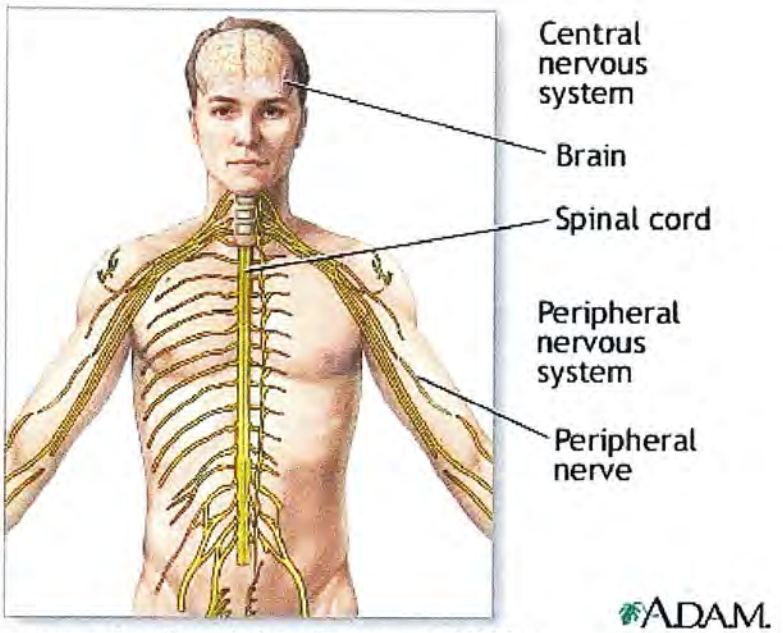
THE PATHOLOGY OF MULTIPLE SCLEROSIS

As has been stated in the main text, MS is a chronic relapsing inflammatory disease of the central nervous system. The correlation between the clinical description and the pathologic process in MS is far from precise, but comprehension of the pathology of the disease helps to explain many of its clinical features and provides the rationale for current approaches to disease treatment. This is an area of complex technical and terminological information, however, this section purports only to outline in brief and using lay terminology the underlying pathology and the residual symptomatology, sufficient in detail relevant to the present study. The interested reader who wishes to find out more information is directed to the following sources on which the information presented in this appendix is mainly based; Tortora & Grabowski, 1996; Herndon, 2000; Multiple Sclerosis Trust, 2004. The first reference provides details of basic anatomy (undergraduate level), the second provides a good source of current evidence and information for professionals on pathology and physiology of MS, and the third source provides excellent details written in lay terminology suitable for patients and other interested parties who do not have training in the area.

The Nervous System

The nervous system is divided into two main systems (*fig.1*); the central nervous system (CNS) which consists of the brain and spinal chord and is enclosed within the skull and backbone, and the peripheral nervous system (PNS) which comprises of all other nerves around the body. The CNS communicates with the muscles and receives information from sensory organs through the PNS that branches throughout the body. This distinction is important as the lesions of MS are strictly confined to the CNS. The CNS performs a great variety of functions, based on the receipt and analysis of information from the outside world and from internal organs, and the initiation and control of response, whether this be movement, emotion, or some more basal activity, such as sweating or emptying the bladder.

Figure 1. The Nervous System

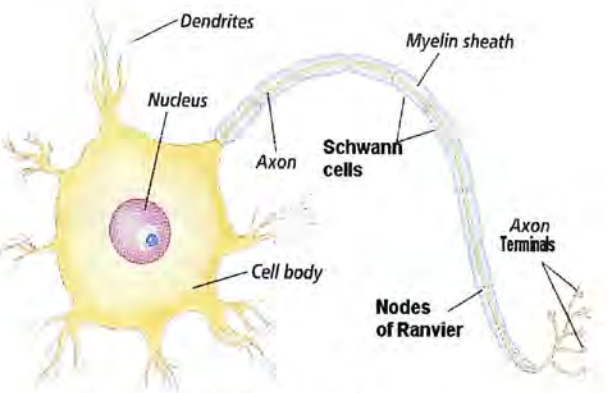


Source: www.nlm.nih.gov/.../ency/imagepages/8679.htm

Neurons

The functions listed above depend on nerve cells or neurons of which the brain contains millions, linked in an orderly but inconceivably complex manner. As figure 2 below shows, each neuron consists of a cell body and a variable number of elongated processes. Information enters the neuron via the dendrites, passes through the cell body and then along the axon until it reaches the synapses where it connects to a dendrite of another neuron. These axons are of particular importance when examining MS. A sheath of fatty protein called myelin surrounds the axon acting as insulation and thus prevents messages becoming interrupted. The myelin sheath has short gaps about one micrometre apart known as Nodes of Ranvier. Nerve messages (nerve impulse) leap along the axon from node to node by means of electrical and chemical changes. The thickness of the myelin sheath and the size of the gap between nodes determine the speed of messages, which can be as fast as 120 meters per second.

Figure 2. The Neuron

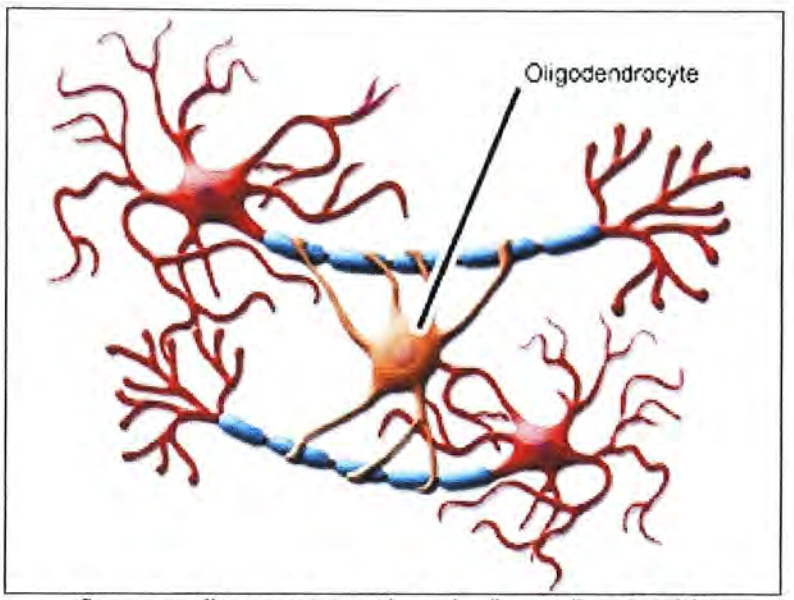


Source: www.emc.maricopa.edu

Support Cells

Approximately forty per cent of the total volume of the brain and spinal cord is made up of cells that support neurons in various ways but which do don't carry information themselves. The collective name for these support cells is glial cells. Glia comes from the Greek word for glue and one of the roles of these cells is to hold the nerve cells in place. Another function of specific glial, oligodendrocytes (fig. 3), is to provide insulation to neurons through the production of myelin. Each oligodendrocyte can supply myelin for several axons and each axon can be supplied by several oligodendrocytes. Any damage to the myelin could lead to the symptoms of MS whereby output can be slower and strained. The analogy of plastic sheath around a copper wire is often used to illustrate the role of myelin; the wire conducts electricity efficiently unless the plastic sheath is damaged, likewise, the myelin sheath is essential for electrical and chemical impulses to be conducted with speed and accuracy.

Figure 3. Oligodendrocytes



Source: mediresource.sympatico.ca/ms/images/img_2-3-4.jpg

The Immune System

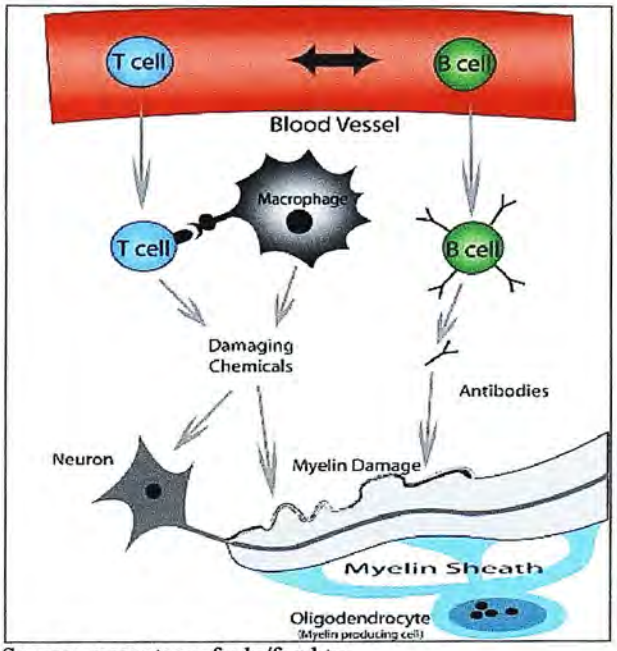
The immune system (fig. 4) is the body's main defence against invasion by infections or other foreign substances. It consists of a collection of special cells and chemicals that patrol the body, identifying and fighting off bacteria, viruses and other invaders that should not be there, leaving the rest of the body untouched.

When a virus or other invading body attacks a cell, the body sends out a chemical as a warning signal and this alerts white blood cells called macrophages. When macrophages encounter a virus or bacterium they encircle and digest it thus rendering it harmless. Macrophages are also called antigen presenting cells, because once some of the invading bugs have been destroyed by the initial immune response, particles of the debris, called antigens, are carried by these cells to another type of white blood cell called T-lymphocytes or T-cells.

There are different types of T-cells. The ones involved in the immune process are called helper T-cells. The helper T-cells respond to the antigen and orchestrate the appropriate response to the invader; they encourage the production of interferons that tell other elements in the immune system how to respond. At the start of an immune

response, messenger molecules called gamma interferon stimulate other types of white blood cell called B-lymphocytes, or B-cells, and killer T-cells. When the foreign body specific to that infection is found, the B-cell clones itself and produces millions of antibodies. Antibodies lock onto the surface of the invading germ thus killing it off. Antibodies stay in the blood following infection creating the 'immune memory'.

Figure 4. The Immune System



Source: mscenter.usf.edu/faq.htm

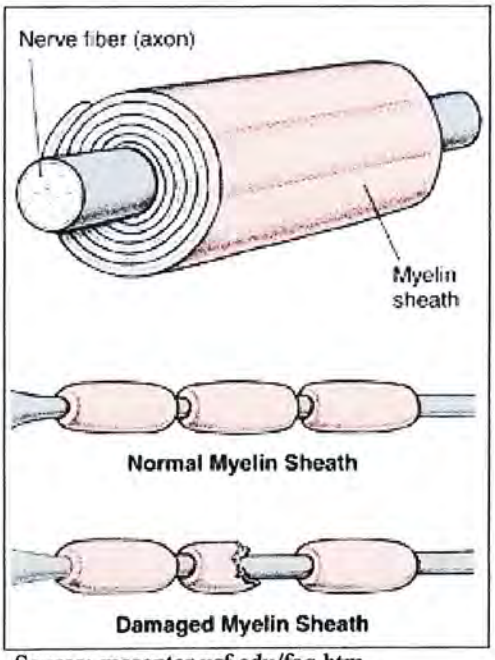
Immune response can result in inflammation of damaged or infected tissue. Inflammation causes local blood vessels to dilate, increasing blood flow to the injured site and bringing with it white blood cells to attack invaders. Killer T-cells kill the body's own cells that have been infected, preventing the germ from reproducing and then infecting other cells. Once the infection is under control, helper T-cells release different messenger molecules called beta interferon that help calm down the immune system.

The Immune System's Terrible Mistake

The cause of MS is unknown. This fact is reiterated here since the auto-immune theory which currently dominates MS research and clinical treatment remains just that, a theory.

It is thought that in MS an autoimmune response leads to the body attacking its own cells. It is suspected that MS is triggered via a viral or bacterial infection that has an antigen which mimics myelin, the fatty protein surrounding the axon. Through a complex process the immune system mistakes the myelin sheath for foreign and begins to destroy it. When myelin is damaged or stripped away from an axon (fig. 5), the messages that pass along it are delayed or blocked. The failure of nerve messages to get through correctly means that bodily functions or processes controlled by the affected nerve pathways do not work properly. Since the CNS controls processes throughout the body and damage can take place anywhere within the CNS, this could account for the wide variance of symptoms.

Figure 5. Damaged Myelin Sheath



Source: mscenter.usf.edu/faq.htm

For reasons that are not yet understood, the attack by the immune system tends to stop after an indefinite period and scar tissue develops on the damaged nerve. The forming of scar tissue over an area of damaged myelin results in plaques or lesions that were first observed by Carswell & Cruveilhier in the 1930s and which show up as white blotches on magnetic resonance imaging (MRI) scans.

Remyelination tends to occur in the earlier stages of MS. Over time, with repeated attacks, oligodendrocytes are damaged and destroyed thus myelin is not replaced. The CNS is able to overcome small areas of axonal loss by finding ways to re-route messages around and area of damage through undamaged cells. However, should this area become too large, this re-routing process is no longer able to compensate and messages to or from that part of the CNS are permanently blocked.

Much of the permanent disability in MS results from axonal destruction, which falls most heavily on very long pathways such as the pyramidal tract supplying the legs and the dorsal columns carrying sensory information from the legs. These long pathways take multiple hits over the years, with increasing axonal destruction leading to the loss of lower extremity function that is so common in advanced MS. Damage in the spinal cord leads to problems of spasticity, weakness, bladder and bowel problems.

Other aspects of the disease, such as incoordination and imbalance, are due to delayed and degraded information resulting from slowed conduction and the inability to monitor motor processes caused by conduction delays and signal dispersion occurring as the signals pass through demyelinated areas. Transient loss of function with fever and with fatigue is also attributable to conduction failure in demyelinating fibres, which fatigue rapidly and fail with an increase in temperature.

Just as there can be a wide variation in physical symptoms due to lesion locations a similar picture of cognitive impairments has also emerged. Within the cerebrum, lesions are most commonly found near the lateral and third ventricles. Frontal lobes are the next most commonly affected, even when the size of the frontal lobes relative to the rest of the brain is considered. Lesions are also frequently observed in other major lobes of the brain. In addition, they are commonly seen in the optic nerves,

chiasm, or tracts, as well as the corpus callosum, brainstem, and cerebellum. The majority of lesions (about 75%) are observed in white matter, but some occur in grey matter and in the junction between grey and white matter (Arnett, 2003).

MS tends to be characterised therefore by demyelination in the subcortical white matter and as a result a number of theorists (Rao, 1986; Ryan *et al.*, 1996) have posited the concept of a subcortical dementia to characterise the pattern of impairments often observed. People with subcortical forms of dementia have relatively intact verbal intelligence and language functioning in comparison to visuospatial and memory skills. Thus the pattern of impairment may resemble that observed in conditions such as Huntington's disease and Parkinson's disease i.e. problems with memory retrieval, abstract reasoning and problem solving, and information processing speed. The concept of subcortical dementia however remains controversial and very much open to debate.

The inclusion of this chapter within the appendices was to provide readers without previous knowledge of the immune system, sufficient information to understand the pathology of MS and how it may cause a variety of symptoms.

Appendix 2

Information Sheets & Consent Forms

(For MS group participants, control group participants, and informants)

Primary and Community Division

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NHS Lothian

MS Group

Research Participant Information Sheet
Version 2a Date 16.04.05

Title: Performance Correlates of Everyday Attention Failures in Multiple Sclerosis (MS)
An examination of sustained attention ability in people with MS

Invitation
You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. If there is anything that is unclear or if you wish more information then you can ask me. Take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of this study
It is thought that in MS is attention is one of the thinking skills most affected, which can have an impact on everyday activities (e.g. work, personal care, social activities). Relatively little research has looked into the impact of changes in thinking ability on everyday activities of patients with MS which is perhaps the most important question from a patient's perspective.

One of the reasons for this is that until recently there have been no adequate measures of attention that can predict the impact on individuals functioning. Three tests of sustained attention have been recently developed which claim to do this but none of them have yet been used within the MS population. The main aim of this study is to find out if people with MS do have sustained attention problems and if so are these tests useful in predicting the impact of attention difficulties in people's lives.

The study will take place between April and August 2005, but each individual will only be required for a one off session lasting no more than one hour. It is hoped that the findings will contribute to a growing understanding of the difficulties faced in MS generally and in turn lead to improved support and treatment in the future.

Why I have I been chosen?
This study is only been carried in Lothian and your consultant neurologist has identified you as potential suitable for this study. It is hoped that there will be 26 individuals with MS recruited into the study, as well 26 without MS.

Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

Primary and Community Division

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NHS Lothian

Version 2 Date 16.04.05
MS group

CONSENT FORM

Title of Project:
An Examination of sustained attention ability in people with Multiple Sclerosis

Name of Researcher: Mr Luke Williams

Please initial/tick box

1. I confirm that I have read and understand the information sheet dated 16.04.05 (version 2a) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that this is part of a research project designed to promote psychological knowledge and which may be of no benefit to me personally. I understand that my General Practitioner will be informed that I have taken part in this study. ☐
4. I agree to take part in the above study. ☐

Name of Participant (Print)	Date	Signature

I confirm that I have explained to the patient/volunteer named above, the nature and purpose of the tests to be undertaken.

Researcher (Print)	Date	Signature

Primary and Community Division

Astley Ainslie Hospital
Department of Clinical Psychology
133 Grange Loan
Edinburgh EH9 2HL
Telephone 0131 537 9000
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Fax **0131 537 9120**
www.show.scot.nhs.uk/lpct/

NHS Lothian

Healthy Volunteer Group

Research Participant Information Sheet
Version 2b Date 16.04.05

Title: Performance Correlates of Everyday Attention Failures in Multiple Sclerosis (MS)
An examination of sustained attention ability in people with MS

Invitation
You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. If there is anything that is unclear or if you wish more information then you can ask me. Take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of this study
It is thought that in MS is attention is one of the thinking skills most affected, which can have an impact on everyday activities (e.g. work, personal care, social activities). Relatively little research has looked into the impact of changes in thinking ability on everyday activities of patients with MS which is perhaps the most important question from a patient's perspective.

One of the reasons for this is that until recently there have been no adequate measures of attention that can predict the impact on individuals functioning. Three tests of sustained attention have been recently developed which claim to do this but none of them have yet been used within the MS population. The main aim of this study is to find out if people with MS do have sustained attention problems and if so are these tests useful in predicting the impact of attention difficulties in people's lives.

The study will take place between April and August 2005, but each individual will only be required for a one off session lasting no more than one hour. It is hoped that the findings will contribute to a growing understanding of the difficulties faced in MS generally and in turn lead to improved support and treatment in the future.

Why I have I been chosen?
Healthy volunteers are required in order to compare the assessment results with those who have MS, thus enabling us to conclude that any differences found between the two groups are due to MS.

Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason.

Primary and Community Division

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NHS Lothian

Version 2 Date 16.04.05
Healthy Volunteer Group

CONSENT FORM

Title of Project:
An Examination of sustained attention ability in people with Multiple Sclerosis

Name of Researcher: Mr Luke Williams

Please initial/tick box

1. I confirm that I have read and understand the information sheet dated 16.04.05 (version 2b) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that this is part of a research project designed to promote psychological knowledge and which may be of no benefit to me personally. ☐
4. I agree to take part in the above study. ☐

Name of Participant (Print)	Date	Signature

I confirm that I have explained to the patient/volunteer named above, the nature and purpose of the tests to be undertaken.

Researcher (Print)	Date	Signature

Primary and Community Division

Astley Ainslie Hospital
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NHS Lothian

Elected known person

Research Participant Information Sheet
Version 2c Date 16.04.05

Title: Performance Correlates of Everyday Attention Failures in Multiple Sclerosis (MS)
An examination of sustained attention ability in people with MS

Invitation
The person who has asked you to complete the questionnaire is one who believes that you know them well. They have asked you to complete this questionnaire as part of a research study that they have volunteered to be a part of. Before you decide whether you are willing to do this it is important that you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. If there is anything that is unclear or if you wish more information then you can ask me. Take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of this study
It is thought that in MS is attention is one of the thinking skills most affected, which can have an impact on everyday activities (e.g. work, personal care, social activities). Relatively little research has looked into the impact of changes in thinking ability on everyday activities of patients with MS which is perhaps the most important question from a patient's perspective.

One of the reasons for this is that until recently there have been no adequate measures of attention that can predict the impact on individuals functioning. Three tests of sustained attention have been recently developed which claim to do this but none of them have yet been used within the MS population. The main aim of this study is to find out if people with MS do have sustained attention problems and if so are these tests useful in predicting the impact of attention difficulties in people's lives.

The study will take place between April and August 2005 and it is hoped that the findings will contribute to a growing understanding of the difficulties faced in MS generally and in turn lead to improved support and treatment in the future.

Why I have I been chosen?
Someone who has volunteered to participate in this research study has chosen you because they believe that you know him or her well. When an individual's ability to sustain attention deteriorates they can sometimes not realise that it has happened. Often people who are close to them notice changes first and can see the impact on their daily functioning. You will be asked to complete a questionnaire about the frequency of everyday mistakes that the person makes e.g. How often do they find themselves suddenly wondering whether they have used a

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www.show.scot.nhs.uk/lpct/

NHS Lothian

Version 2 Date 16.04.05
Elected Known Person

CONSENT FORM

Title of Project:
An Examination of sustained attention ability in people with Multiple Sclerosis

Name of Researcher: Mr Luke Williams

Please initial/tick box

1. I confirm that I have read and understand the information sheet dated 16.04.05 (version 2c) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that this is part of a research project designed to promote psychological knowledge and which may be of no benefit to me personally. ☐
4. I agree to take part in the above study. ☐

Name of Participant (Print)	Date	Signature

I confirm that I have explained to the patient/volunteer named above, the nature and purpose of the tests to be undertaken.

Researcher (Print)	Date	Signature

Appendix 3

SART Stimuli

Example Stimuli from Sustained Attention to Response Task (SART)

Masking Symbol, presented between presentation of each digit stimulus

The five possible font sizes of the digits presented: actual stimulus used digits 1-9

3 3 3 3 3

Appendix 4

Cognitive Failures Questionnaire

(Self and Informant Versions)

The Cognitive Failures Questionnaire (Broadbent, Cooper, Fitzgerald & Parkes, 1982)

The following questions are about minor mistakes which everyone makes from time to time, but some of which happen more often than others. We want to know how often these things have happened to you in the past 6 months. Please circle the appropriate number.

		Very often	Quite often	Occasionally	Very rarely	Never
1.	Do you read something and find that you haven't been thinking about it and must read it again?	4	3	2	1	0
2.	Do you find that you forget why you went from one part of the house to the other?	4	3	2	1	0
3.	Do you fail to notice signposts on the road?	4	3	2	1	0
4.	Do you find that you confuse right and left when giving directions?	4	3	2	1	0
5.	Do you bump into people?	4	3	2	1	0
6.	Do you find you forget whether you have turned off a light or a fire or locked the door?	4	3	2	1	0
7.	Do you fail to listen to people's names when you are meeting them?	4	3	2	1	0
8.	Do you say something and realise afterwards that it might be taken as insulting?	4	3	2	1	0
9.	Do you fail to hear people speaking to you when you are doing something else?	4	3	2	1	0
10.	Do you lose your temper and regret it?	4	3	2	1	0
11.	Do you leave important letters unanswered for days?	4	3	2	1	0
12.	Do you find you forget which way to turn on a road you know but rarely use?	4	3	2	1	0
13.	Do you fail to see what you want in a supermarket (although its there)?	4	3	2	1	0
14.	Do you find yourself suddenly wondering whether you have used a word correctly?	4	3	2	1	0

PTO

INFORMANT VERSION

The Cognitive Failures Questionnaire (Broadbent, Cooper, Fitzgerald & Parkes, 1982)

The following questions are about minor mistakes which everyone makes from time to time, but some of which happen more often than others. We want to know how often these things have happened to your relative/friend/or person you care for in the past 6 months. Please circle the appropriate number.

		Very often	Quite often	Occasionally	Very rarely	Never
1.	Do they read something and find that they haven't been thinking about it and must read it again?	4	3	2	1	0
2.	Do you find that they forget why they went from one part of the house to the other?	4	3	2	1	0
3.	Do they fail to notice signposts on the road?	4	3	2	1	0
4.	Do you find that they confuse right and left when giving directions?	4	3	2	1	0
5.	Do they bump into people?	4	3	2	1	0
6.	Do you find they forget whether they have turned off a light or a fire or locked the door?	4	3	2	1	0
7.	Do they fail to listen to people's names when they are meeting them?	4	3	2	1	0
8.	Do they say something and realise afterwards that it might be taken as insulting?	4	3	2	1	0
9.	Do they fail to hear people speaking to them when they are doing something else?	4	3	2	1	0
10.	Do they lose their temper and regret it?	4	3	2	1	0
11.	Do they leave important letters unanswered for days?	4	3	2	1	0
12.	Do they find they forget which way to turn on a road they know but rarely use?	4	3	2	1	0
13.	Do they fail to see what they want in a supermarket (although its there)?	4	3	2	1	0
14.	Do they find themselves suddenly wondering whether they have used a word correctly?	4	3	2	1	0

PTO

Appendix 5

Lothian Research Ethics Committee Approval Letter

Lothian NHS Board

Deaconess House
148 Pleasance
Edinburgh
EH8 9RS
Telephone 0131 536 9000
Fax 0131 536 9009
www.nhslothian.scot.nhs.uk

NHS Lothian

Lothian Local Research Ethics Committee 02

23 May 2005

Mr L Williams
Trainee Clinical Psychologist
NHS Lothian
Astley Ainslie Hospital
Department of Clinical Psychology
133 Grange Loan, Edinburgh
EH9 2HL

Dear Mr Williams

Full title of study: ***Performance correlates of everyday attention failures in people with Multiple Sclerosis***
REC reference number: ***05/S1102/17***
Protocol number:

Thank you for your letter of 21 April 2005, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type:	Version:	Dated:	Date Received:
Application	1	18/03/2005	21/03/2005
Investigator CV		18/03/2005	21/03/2005
Protocol	1	18/03/2005	21/03/2005
Covering Letter		18/03/2005	21/03/2005
Copy of Questionnaire Validated		18/03/2005	21/03/2005
GP/Consultant Information Sheets		20/05/2005	22/04/2005
Participant Information Sheet	2b	16/04/2005	22/04/2005
Participant Information	2	16/04/2005	22/04/2005

23 May 2005

University of Edinburgh
Department of Psychiatry
Kennedy Tower
Royal Edinburgh Hospital
E10 5HF

Dear Sir,

Full title of study: ***Performance correlates of everyday attention failures in people with Multiple Sclerosis***

REC reference number: ***05/S1102/17***

Protocol number:

The Research Ethics Committee has reviewed the above application in accordance with the standard operating procedures for RECs.

The Committee has issued a favourable ethical opinion of the application.

The Chief Investigator has been notified of the Committee's opinion in our letter of 23 May 2005. The letter gives full details of the documents reviewed.

Statement of compliance

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

05/S1102/17	**Please quote this number on all correspondence**

Yours sincerely

Miss Lyndsay Baird
Secretariat Support Officer
Committee Administrator

E-mail: lyndsay.baird@lhb.scot.nhs.uk

Lothian Local Research Ethics Committee 02

LIST OF SITES WITH A FAVOURABLE ETHICAL OPINION

For all studies requiring site-specific assessment, this form is issued by the main REC to the Chief Investigator and sponsor with the favourable opinion letter and following subsequent notifications from site assessors. For issue 2 onwards, all sites with a favourable opinion are listed, adding the new sites approved.

REC reference number:	05/S1102/17	**Issue number:**	1	**Date of issue:**	23 May 2005
Chief Investigator:	Mr L Williams				
Full title of study:	Performance correlates of everyday attention failures in people with Multiple Sclerosis				

This study was given a favourable ethical opinion by Lothian Local Research Ethics Committee 02 on 01 June 2005. The favourable opinion is extended to each of the sites listed below. The research may commence at each NHS site when management approval from the relevant NHS care organisation has been confirmed.

Principal Investigator	Post	Research site	Site assessor	Date of favourable opinion for this site	Notes [1]
Mr L Williams	Trainee Clinical Psychologist	Astley Ainslie Hospital, Liberton Hospital and Western General Hospital	Lothian Local Research Ethics Committee 02	23/05/2005	

Approved by the Chair on behalf of the REC:

.... (Signature of Chair/Administrator*)

..... (Name)

[1] *The notes column may be used by the main REC to record the early closure or withdrawal of a site (where notified by the Chief Investigator or sponsor), the suspension of termination of the favourable opinion for an individual site, or any other relevant development. The date should be recorded.*

Sheet			
Participant Information Sheet	2a	16/04/2005	22/04/2005
Participant Consent Form	2	16/04/2005	22/04/2005
Participant Consent Form	2	16/04/2005	22/04/2005
Participant Consent Form	2	16/04/2005	22/04/2005
Response to Request for Further Information		21/04/2005	22/04/2005
Supervisors CV		18/03/2005	21/03/2005

Management approval

The study should not commence at any NHS site until the local Principal Investigator has obtained final management approval from the R&D Department for the relevant NHS care organisation.

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Notification of other bodies

The Committee Administrator will notify the research sponsor that the study has a favourable ethical opinion.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

05/S1102/17	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project,

Yours sincerely,

Chair

E-mail:

Enclosures *Standard approval conditions*

Site approval form (SF1)